

## Biological Activities of Resveratrol against Cancer

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### Abstract

Resveratrol (RSV) is a polyphenolic compound naturally found in grapes, peanuts, and berries. Considerable research has been performed to determine the benefits of RSV against various human diseases, especially cancer. Despite numerous studies on the effect of RSV on cancer, correct understanding of its mechanism is still far from certainty. This review summarizes the recent results on the molecular mechanisms and pathways of actions of RSV against major cancers. According to investigations accomplished worldwide, RSV targets pathways such as cell cycle progression, autophagy, apoptosis, angiogenesis and invasion/metastasis to attenuate cancer progression mediated through PI3K/Akt/mTOR, Wnt, ROS, NF- $\kappa$ B, BAX/Bcl-2, AMPK, ERK, MAPK signaling pathway. Considering the side-effects and data of clinical trials, RSV can be used for its maximum benefits in human diseases. Available published data provide strong clues on the impact of RSV on cancer management.

**Keywords:** Resveratrol; Gastric cancer; Esophageal cancer; Breast cancer; Lung cancer; Colon cancer

### Introduction

Resveratrol (trans-3,4,5-trihydroxystilbene, RSV) is a polyphenol that is naturally found in berries, peanuts, and grapes and is produced in response to mechanical injury, fungal infection, and ultraviolet radiation [1]. The concentration of RSV is 32 ng/g in blueberries, 1,920 ng/g in peanuts, and 3,540 ng/g in grapes [2,3]. *Polygonum cuspidatum*, a Japanese plant, was found to have the highest level of natural RSV and used for several ailments including inflammation [4]. In 1997, Jang first demonstrated that external application of RSV prevented tumorigenesis in skin cancer model mice; thereafter, numerous investigations followed [5]. Compared to high-fat diet, supplemental RSV showed beneficial effects and provided more energy in animal models [6-8]. Several publications have shown that RSV had multiple anticancer effects, such as protection against tumor initiation and cancer progression, apoptosis, antioxidant, anti-angiogenesis, anti-inflammatory, and anti-tumor migration [9-12]. In further investigations, application of RSV on the skin surface of mouse models of skin tumorigenesis revealed healing of the ailments by inducing apoptosis, controlling the cell cycle, and hindering COX activity [9-11]. One major disadvantage of RSV is its bioavailability, which has been proven to be less than 1 mg/ml [12]. Therefore, various strategies have been used to enhance the solubility and bioavailability of RSV with the use of microparticles [13], cyclodextrin complexes [14], or nanoparticles [15,16] RSV has been found to possess potent antioxidant properties of ROS inhibition, AMPK activation, and suppression of lipid peroxidation [17]. Oxidative stress is the result of alteration of balance between ROS production and consumption by antioxidant activity [18].

Moreover, RSV has been reported to protect different animal models against atherogenesis [19] and enhanced vasodilation by increasing the activity of endothelial nitric oxide synthase [20]. Another study on a pig model revealed that RSV could prevent cardiovascular diseases by enhancing myocardial perfusion and decreasing oxidative stress [21]. According to studies in the last decade, RSV exhibited neuroprotective [22] antidiabetic [23], radioprotective and cytogenetic [24] characteristics. Importantly, RSV has been reported to be effective in cancer [25]. The anti-tumor effect of RSV is linked with its ability to regulate reactive oxygen species and cellular processes such as apoptosis, and both cancerous cell proliferation and differentiation. Therefore, in this review, we focus on the characteristics of RSV and

molecular mechanism involved in the therapeutic role of RSV against cancers which, because of a wide spectrum of biological activities may be used in the prevention of cancer. We have summarized the regulation of cell cycle regulation, invasion/metastasis, angiogenesis and induced apoptosis and autophagy mediated through the regulated cell cycle-associated proteins; induced BCL-2/BAX and AMPK; inhibited the PI3K/Akt/Mtor, WNT, MEK, ERK pathways by resveratrol in different cancers. We have discussed the importance of these signaling pathways in cancer progression, along with their modulation by RSV.

### Resveratrol and head and neck cancer

Head and neck cancer is the sixth most common cancer and is the eighth leading cause of death in the world [26]. An *in vitro* study on human head and neck cancer cells revealed that RSV downregulated various STAT-3-related gene expressions and inhibited proliferation, invasion, and cell cycle arrest, including apoptosis, through induction of SOCS-1 mRNA and protein [25]. Another investigation showed that combination of RSV and curcumin inhibited *in vitro* and *in vivo* cancer growth by increasing PARP cleavage and BAX/BCL-2 ratio and by inhibiting ERK1 and ERK2 phosphorylation [27]. Moreover, RSV treatment was shown to inhibit cell viability, induce apoptosis of C666-1 cells by cleavage of caspase-3, and regulate Bax/BCL2 apoptotic signaling through activation of AMPK activity [28]. In an *in vitro* study on human nasopharyngeal cancer, RSV treatment upregulated caspase-3 protein, but downregulated the expressions of BCL-2 and hypoxia-inducible factor-1 $\alpha$  (HIF-1  $\alpha$ ) protein and decreased the phosphorylation of Akt1, p70S6K, p-4EBP1, and cell cycle regulatory proteins to inhibit cancer progression [29]. In a study on nasopharyngeal carcinoma cells HT1376 and Hep3B, RSV was reported to inhibit cell survival and have anti-apoptotic mechanisms by suppressing NP63 expression; these suggested that NP63, not P53, was a molecular target

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of RSV [30]. RSV decreased cell growth and increased chemo- and radiosensitivity including cancer invasion of head and neck squamous cell carcinoma (HNSCC) cells which illustrated the anticancer property of RSV is mediated through regenerating gene (REG) III expression pathway [31]. Feng treated Pterostilbene, a dimethylated resveratrol to human esophageal squamous cancer (EC109) cells and observed its anticancer effects such as decrease in cell viability, adhesion, migration and caspase-3 activity and increase in endoplasmic reticulum stress (ERS) related molecules (such as GRP78, ATF6, p-PERK, p-e12F-alpha and CHOP) and concluded that the anticancer activity is due to the triggering of ERS signaling pathway [32]. A study of oral squamous cell carcinoma showed that RSV significantly increased apoptosis and cell cycle arrest at G2/M phase of SCC-VII, SCC-25 and YD-38 cells in a dose- and time- dependent manner [33]. In an oral cancer (SCC-9) cells, RSV treatment prevented expression of MMP-9 protein, in addition to inhibition of the JNK1/2 and ERK1/2 signaling pathway [34]. RSV proved to be cytotoxic by reducing cell migration ability and increasing cell cycle arrest and showed synergistic effect combined with irradiation in oral squamous cell carcinoma (PE/CA-PJ15) cells [35], also, an *in vitro* study showed that RSV inhibited adhesion, migration and invasion of OSCC cells [36]. A study of human nasopharyngeal carcinoma cells showed that inhibiting autophagy by ATG7-siRNA and bafilomycinA1 increased the apoptotic cell death via increasing the endoplasmic stress and caspase-12 [37]. In an research conducted in a C57BL/6 mice in which tongue tumorigenesis is induced by 4-nitroquinoline-1-oxide (4NQO) revealed that mice fed with grape seed extract or RSV had decreased tumor incidence compared to that of control through regulating AMPK activation thereby inducing apoptosis and autophagy [38]. RSV is found to inhibit cell growth and promote cell differentiation in anaplastic thyroid carcinoma (ATC) cells by activating Notch1 signaling [39]. Hu found that RSV suppressed invasiveness or anchorage independent growth of head and neck cancer cells regulated by several EMT markers *in vitro* and also reduced tumor growth *in vivo* in head and neck cancer mice model [40]. RSV was found to inhibit cell growth, induce DNA damage and apoptosis in HNSCC cells independent of Smad4 expression in both *in vivo* and *in vitro* studies [41]. Study of medullary thyroid (MTC) cancer showed that when RSV is treated to MTC cells, it suppressed cell growth via caspase-3 dependent apoptosis and decreased ASCL1 and chromogranin whereas induced Notch2 expression [42]. A study showed that RSV induced apoptosis in human nasopharyngeal cancer cells by regulating multiple apoptotic pathways including death receptor, mitochondria and ER stress [43]. In a study of UMSSC-22B cells, RSV was found to induce apoptosis and COX-2 accumulation in nucleus which leads to p53 activation and p53 dependent apoptosis [44]. A study of thyroid cancer revealed that RSV treatment increase p53 expression and p53 dependent apoptosis via Ras-MAPK signaling pathway [45].

### Resveratrol and esophageal cancer

A study in a Swedish population showed that a dietary pattern that included RSV might have a protective role in the development of esophageal cancer [46]. Another research showed that RSV caused death of esophageal squamous cell carcinoma cells by inhibiting cell cycle progression at the sub G1 phase and by inducing apoptosis [47]. Treatment of esophageal cancer cells- EC109 with pterostilbene, a RSV analog, reduced tumor cell adhesion, migration, and intracellular glutathione and increased the apoptotic index, caspase-3 activity, and ROS levels [32]. In an F344 rat model of esophageal tumorigenesis induced by N-nitroso methyl benzylamine, oral and intraperitoneal RSV treatment at 2 mg/kg and 1–2 mg/kg, respectively, reduced the

number of tumors by inhibiting COXs and prostaglandin E2 [48]. Zhou showed that RSV inhibited the growth of EC-9706 in a dose- and time-dependent manner through apoptosis by downregulating the expression of Bcl-2 gene and upregulating the expression of Bax-gene [49]. Another study showed that RSV suppressed esophageal adenocarcinoma cell proliferation by p27kip1 upregulation, which is controlled by downregulations of S-phase kinase-associated protein 2 and 26s proteasome [50]. In a study, a group of 31 rats treated with RSV for 5 months reported decreased degree of esophagitis and incidence of intestinal metaplasia and carcinoma compared with the control group showing its chemo preventive property [51]. Similarly, Szumilo also showed the chemopreventive property of RSV in rats that are exposed to chemical carcinogens [52].

### Resveratrol and gastric cancer

Gastric cancer (GC) is the second most common cause of cancer-associated mortality [53] because it is difficult to be detected in the early phase. Since it is usually diagnosed in the advanced stages, prognosis is poor despite the availability of therapies such as surgery, chemotherapy, and radiotherapy [54]. RSV can prevent *Helicobacter pylori* infection by inhibiting its growth. It also decreases oxidative stress by inhibiting *H. pylori* induced ROS production, which is a cause of cancer [55]. *In vivo* studies on nude mice demonstrated that RSV administration to the site of tumor formation significantly inhibited both GC progression [56] and carcinoma growth via apoptosis [57]. RSV reversed the doxorubicin resistant property of SGC7901/DOX cells back to doxorubicin sensitive cells which resulted to reduced migration/invasion, increased apoptosis *in vitro* and prevented tumor growth *in vivo*, moreover RSV inhibited AKT pathway to reverse the epithelial-mesenchymal transition (EMT) [58]. Jing showed that RSV prevented gastric cancer cell growth by inhibiting cell cycle in MGC803 cells by suppressing PTEN/PI3K/AKT signaling pathway [59]. The *in vitro* experiments performed by Gao revealed that RSV reduced invasion and metastasis in gastric cancer cells by hindering Hedgehog signaling pathway and EMT [60]. In an *in vitro* study, RSV caused cell cycle arrest, induced apoptosis and reduced expression level of surviving inhibiting the proliferation of gastric cancer SGC7901 cells [61]. When gastric cells were exposed to RSV in combination with dimethyl sphingosine (DMS) the cytotoxicity due to RSV accentuated depicting that inhibition of sphingolipid metabolism enhances RSV chemotherapy in human gastric cancer (SNU-1 and HT-29) cells [62]. Further, Wang found that RSV caused increased production of ROS resulting in apoptosis and DNA damage in GC (SGC7901) cells while no effect was observed in sirtuin1 level [63]. When gastric adenocarcinoma cells were treated with RSV, the number of micronuclei observed in the cells increased dose-dependently showing RSV's genotoxic role [64]. In a study of gastric cancer cells, RSV was found to mimic a role of dihydroceramide desaturase inhibitor which resulted in accumulation of dihydroceramide in cells that concluded that RSV ultimately induced autophagy via dihydroceramide in HGC-27 cells with no apoptosis [65]. A study by Aquilano found that to suppress proliferation of human adenocarcinoma gastric cancer (AGS), trans-resveratrol inhibited phosphorylation of ERK1/2 via MEK1/2 ultimately repression of c-Jun activation [66]. Moreover, RSV combined with garlic oil induced apoptosis via upregulation of Fas protein and bax gene and downregulation of bcl-2 gene [67]. In another investigation, it was found that apoptotic signaling pathway of different cells of gastric adenocarcinoma cells responded differently to the treatment of RSV, for example, in SNU-1 cells, RSV downregulated survivin, however, activation of caspase-3 and cytochrome C oxidase activities was observed in AGS and KATO-III cells in response to

RSV treatment [68]. Similar research in gastric adenocarcinoma cells showed that RSV induced apoptosis and increased expression level of tumor suppressors p21 and p53 accompanied by cell cycle arrest at S to G(2)/M phases, the SNU-1 cells treated with RSV responded with up-regulation of both Fas and Fas-L proteins, but p53 knocked out KATO-III cells showed elevated expression of Fas-L suggesting that RSV has chemopreventive properties against gastric adenocarcinoma cells via different approaches depending upon the cell type of the cancer [69]. Additionally, inhibitory and chemopreventive effect of RSV against gastric adenocarcinoma (SNU-1) cells may be due to the ability of RSV to produce NO from NOS showing its antioxidant action [70]. Atten investigated phosphotransferase activities of two key signaling enzymes- Protein kinase C (PKC) and mitogen-activated protein kinases (ERK1/2) in KATO-III and RF-1 cells, RSV induced cell cycle arrest, apoptosis and significantly inhibited PKC activity of KATO-III cells and of human recombinant PKC-alpha but no effect on ERK1/2 [71].

### Resveratrol and colorectal cancer

Although the number of cases has declined owing to better detection and screening methods, colorectal cancer remains one of the leading causes of cancer deaths in western countries [72]. Nutrition, food habit, and lifestyle substantially influence the development of colorectal cancer [73]. A study found that RSV inhibited proliferation of colorectal cancer cells and diminished drug resistance by downregulating the NF- $\kappa$ B pathway and inhibiting epithelial-mesenchymal transition (EMT)-associated molecules, such as the mesenchymal marker vimentin and the transcription factor Slug, whereas upregulating the epithelial marker E-cadherin [74]. RSV increased the phosphorylation and caused the proteasomal degradation of T-cell factor 4, resulting in the suppression of beta-catenin- and TCF-mediated transcriptional activity; these events increased apoptosis in human colorectal cancer cells [75]. RSV extracted from *Polygonum cuspidatum* was reported to prevent invasion and metastasis of colorectal cancer cells by inhibiting the Wnt/beta-catenin signaling pathway through regulation of the expression of metastasis-associated lung adenocarcinoma transcript1 [76]. RSV was shown to initiate endoplasmic stress, which eventually resulted in apoptotic death of colorectal cancer (HT 27) cells [77]. Wolter found that RSV exhibited chemotherapeutic effect against colon cancer cells by cell cycle arrest through downregulation of the cyclinD1/CDK4 complex [78]. Another study concluded that Sirt1 signaling pathway was one of the main mechanisms by which RSV exerted its effects on colorectal cancer cells [79]. Karimi discovered that qRT-PCR and western blot analysis of LNA-anti0miR-200c transfected cells showed increased expression level of vimentin and ZEB-1 along with reduced expression level of E-cadherin which caused increase in the migration of HCT-116 cells but treatment of RSV reversed EMT to MET phenotype by upregulating mir-200c in colorectal cancer cells [80]. Sonic hedgehog (Shh) protein increased the proliferation and migration rate of HCT-116 cells and increased expression level of Ptch, Smo and Gli-1 protein, but after treatment of RSV the cell viability and migration rate decreased via suppression of Ptch, Smo and Gli-1 protein level [81]. A research by Feng demonstrated that RSV significantly inhibited cell proliferation of colon cancer cells (HCA-17, SW480, HT29) cells by inducing apoptosis and inhibiting expression of cyclooxygenase-2 and prostaglandin receptor [82]. Yang found that RSV suppressed colorectal cancer by upregulating miR-34c which successively was able to inhibit its target KITLG, this effect was accentuated in presence of p53 compared to p53-knockdown cells *in vitro* and *in vivo* [83]. RSV significantly showed anti-cancer effect by upregulating expression level of BMP9 in LoVo cells, moreover,

when p38 MAPK was inhibited, it partly reduced the anticancer effect of RSV but however anticancer effect was significantly lost by using BMPR inhibitor suggesting the anticancer property of RSV in LoVo cells is BMPR dependent [84]. An interesting study regarding RSV dose-response relationship on a mice model of colorectal cancer found that low RSV dose repressed the cancer development more efficiently than 200 times higher dose by activating AMPK and upregulating the expression of the p21 protein [85]. The colorectal cancer stem cells (CCSC) induced from HCT116 cells when treated with RSV resulted in decreased CCSC proliferation in a dose and time dependent manner, cell cycle arrest at G0/G1 phase and apoptosis including the upregulation of MICA/B expression to enhance cell immunogenicity [86]. Demoulin showed that RSV inhibited cell growth progression of HCT-116 by inducing apoptosis, activating p53 and DNA damage via type-II topoisomerase poisoning [87]. Clinical studies of colorectal cancer showed that RSV reduced cancer cell growth [88] by controlling the expression of WNT pathway target genes [89] and by increasing apoptosis in cancer tissues [90]. Another study by Ji confirmed that RSV inhibited the migration and invasion of LoVo cells in a dose dependent manner by elevating the expression of E-cadherin and suppressing the expression of Vimentin, along with the inhibition of TGF-beta1/smads signaling pathway [91]. In an *in-vivo* study, mice fed with 150 - 300 ppm RSV demonstrated 60% inhibition of tumor production and in the remaining 40% of mice developed tumors which had lost Kras expression whereas in a therapeutic assay where mice had developed tumor showed complete disappearance of tumors in 33% of mice and 97% decrease in tumor size in remaining mice. In addition, RSV inhibited the expression of Kras expression which prevented the formation and growth of colorectal tumors [92]. Another study found that RSV when treated in combination with mitomycin M enhanced the anticancer effects of MMC through upregulation of P21 (WAF1/CIP1) causing the cell cycle arrest at G0/G1 and G2/M phases [93]. Study on HCT116 and Caco-2 cells revealed that RSV induced cell cycle arrest and apoptosis via caspase dependent cyclin-CDK pathways [94]. A study on colon cancer HCT116 cells showed that RSV hindered cell proliferation *in vitro* including in a xenograft tumor via upregulating expression of PTEN whereas decreasing phosphorylation of AKT, and the expression of protein and mRNA of beta-catenin are decreased by RSV in a dose dependent manner suggesting the involvement of WNT/beta-catenin pathway [95]. A systematic study of activity of RSV on colorectal cancer cells - HCT116 and Caco-2 cells demonstrated an excellent anti-cancer property of RSV through downregulation of glycolytic enzymes, expression of leptin and c-Myc and content of vascular endothelial growth factor whereas the apoptotic markers were upregulated in the colorectal cancer cells which were calorie deprived suggesting that calorie restriction pathway may be the basis of the cell death [96]. Miki H found that RSV increased intracellular reactive oxygen species (ROS) causing increase in autophagy that induced caspase dependent apoptosis in HT-29 and COLO 201 cells, suggesting that autophagy also mediated the apoptosis in human colon cancer cells [97]. Study by Radhakrishnan found that RSV increased the apoptosis of colon cancer cells induced by grape seed extract through the apoptotic pathway involving P53 and Bax: bcl-2 ratio [98]. Vanamala showed that proliferation of insulin like growth factor-1 (IGF-1) induced apoptosis via downregulation of IGF-1R/Akt/Wnt signaling pathways and by activation of P53, showing RSV's anticancer effect [99]. When RSV and tannic acid is treated to Caco-2 cells, apoptotic index, Bak protein percentage ratio, and FADD protein % ratio values increased in a dose and time dependent manner inducing apoptosis in mitochondrial and death receptor pathways [100]. A study of effect of RSV on HT-29 cells showed that RSV induced apoptosis



via mitochondria apoptosis pathway triggered by production of ROS [101]. Another *in vitro* study revealed that RSV caused apoptosis in human colon cancer cells (HT-29 and WiDr) in a dose-dependent manner including downregulation of telomerase activity (TLMA) in colon cancer cells [102]. Interestingly, a study showed that RSV activated caspase-2 upstream of mitochondria which is not dependent upon anti-oxidant property of NF-kappaB inhibition but induced conformational changes in Bax/Bak with subsequent release of cytochrome-C, apoptosis-inducing factor, and endonuclease-G [103]. Moreover, low concentration of RSV caused co-localization of Bax protein with mitochondria, collapse of mitochondrial membrane potential, activation of caspases resulting to apoptosis [104]. The results of a study on SW480 show that RSV inhibited the cell growth by hindering cell cycle at S phase by accumulation of cyclin A and B1 along with CDK1 and CDK2 [105].

### Resveratrol and liver cancer

Hepatocellular cancer is the sixth most common cancer and the second leading cause of cancer death [106]. The major cause of hepatocellular cancer is infection with hepatitis B and hepatitis C virus. Diet and lifestyle were also considered as possible risk factors of liver cancer [107]. A study reported that RSV inhibited the growth of HepG2 cells by decreasing the levels of cyclin D1, possibly by inhibiting the levels of p38 MAP kinases and the AKT pathway [108]. Analysis of the cell cycle in liver cancer murine models showed that treatment with RSV at 10 and 15 mg/kg body weight significantly inhibited liver cancer by 36.3% and 49.3%, respectively by decreasing expression of cyclinB1 and p34cdc2 protein [109]. A similar study on a murine model of liver cancer showed that RSV, in addition to 5-FU treatment, induced an S-phase arrest of H22 cell growth and enhanced the antitumor effects of chemotherapy [110]. One research on HepG2 cells exposed to high glucose conditions to mimic a diabetic condition revealed that RSV (100  $\mu$ M) suppressed the proliferation of HepG2 cells by inhibiting the STAT3 and Akt signaling pathways [111]. Zhang found that RSV significantly decreased the proliferation of HepG2 cells and exerted its antitumor effect by suppressing the expression of the vascular endothelial growth factor (VEGF) gene [112]. In an *in vitro* investigation of HepG2 hepatocellular carcinoma cells, a RSV analog known as phoyumbene B was found to be more effective than RSV in inhibiting cell proliferation by inducing G2/M cell cycle arrest and apoptosis by downregulating Bcl-2 and upregulating Bax, moreover, inhibition of invasion ability of the cells was also reported [113]. A study showed significant anticancer activity when RSV was treated in combination with curcumin by caspase activation and upregulation of ROS [114]. In a study the hepatocellular cancer (HCC) cells were found to have higher expression of Myosin light chain kinase (MLCK) but RSV treatment downregulated MLCK expression which triggered apoptosis and suppressed tumorigenesis suggesting MLCK might be linked with occurrence of HCC [115]. High expression of urokinase (uPA) is correlated with high malignancy, in a study, RSV is reported to inhibit uPA expression and metastasis of HCC by downregulating transcription factors of SP-1 signaling pathway [116]. In a rat hepatoma cell line, RSV was found to inhibit phosphorylation of mTOR and hence suppressing the protein synthesis to hinder liver cancer progression [117]. Another study concluded that the anticancer property of RSV in HCC occurred due to upregulation of p-JNK expression while downregulation of p-ERK expression *in vitro* and *in vivo* [118]. An investigation using male wistar rats revealed that administration of RSV at early or late stage of the liver cancer significantly decreased carcinogenesis via inducing apoptotic pathway [119]. Weng investigated the effect of RSV and its analog on HCC and

discovered the anti-invasive property of RSV which decreased protein expression of MMP-9 and MMP-2 while increased the expression of TIMP-1 and TIMP-2 [120]. Bishayee discovered that treatment of RSV can inhibit hepatocarcinogenesis induced by diethylnitrosamine (DEN) in Sprague-Dawley rats by apoptotic pathway mediated through downregulation of BCL-2 and upregulation of Bax expression [121] similar study showed that RSV caused chemoprevention of hepatocarcinogenesis by decreasing expression levels of heat shock protein (HSP70), COX-2 and NF-kappaB [122]. Study by Yu HB concluded that RSV hindered growth of HepG2 cells by suppressing VEGF activity via inactivation of NF-kappaB, along with inhibition of tumor growth and angiogenesis [123]. RSV inhibited cell growth of Huh-7 cells by downregulating cyclinE, cyclinA and CDK-2 while upregulating P21/WAF1 expression in a p53 dependent manner [124]. Moreover, similar effect was seen in HepG2 cells line RSV inhibited growth of rat and human hepatoblastoma cells by restricting the cell cycle progression [125]. Additionally, the synergistic effect of alcohol enhanced the cytotoxicity [126]. The synergistic anti-cancer effect of RSV and 5-FU increased than compared to the each compound treated alone in hepatoma H22 cells [127]. Yu found that RSV suppressed TNF-alpha dependent MMP-9 expression and invasion of HCC partly via downregulation of NF-kappaB signaling pathway [128]. In a study, dietary RSV was found to have a hypolipidemic property along with anti-cancer and anti-metastatic effects against hepatoma in Donyu Rats [129]. Another study of hepatoma showed the anti-invasive as well as anti-oxidative activity of RSV but no sign of inhibition of cell growth of hepatoma AH109A cells *in vitro* and *ex vivo* environment [130]. In an investigation RSV is reported to reduce ROS production and inhibit cell growth through apoptosis and cell cycle arrest however it also increases iNOS, eNOS and hence increases NOS activity [131]. A recent study revealed that a dimethylated derivative of RSV known as pterostilbene was able to induce caspase-3 and ROS dependent mitochondrial apoptotic pathway which resulted to inhibition of tumor progression in HCC [132]. Study on HCC has discovered that RSV decreased hepatocyte growth factor-induced invasion of HepG2 cell invasion by an unknown mechanism [133]. RSV suppressed proliferation of HCC cells in dose-dependent manner by inhibiting c-Met signaling pathway *in vitro* in addition to significant inhibition of tumor growth *in vivo* in a xenograft model [134].

### Resveratrol and prostate cancer

Prostate cancer is the most common cancer in men and a major cause of cancer deaths [135]. A study showed that RSV inhibited Akt, an upstream regulator of the miR-21 gene in PC-3M-MM2 cells, to reduce the viability and invasiveness of a tumor *in vitro* as well as *in vivo* [136]. Another research found that RSV treatment reduced lipopolysaccharide-induced markers of EMT and inhibited the expression of Gli1; these findings showed the inhibitory effect of RSV on PC-3 and LNCaP cell lines [137]. Moreover, RSV was reported to inhibit nuclear translocation of beta-catenin by decreasing HIF-1alpha expression, which leads to the suppression of tumor growth of castration-resistant prostate cancer [138]. Ganapathy concluded that RSV was a potential drug for prostate cancer because it inhibited tumor growth, metastasis, and angiogenesis by enhancing the therapeutic efficacy of TRAIL through activation of the FOXO transcription factor [139]. In addition, Benitez DA suggested that both the anti-proliferative and apoptotic effects of RSV on human prostate cancer cells were mediated by inactivation of NF-kB activity, which was associated with PI3K inhibition [140]. RSV in combination with docetaxel when treated resulted to apoptosis and cell cycle arrest via upregulation of P53 expression and cell cycle inhibitors such as P21, WAF1, CIP1, and

P27KIP in prostate cancer cells [141]. In a study of murine model of prostate cancer, RSV was found to decrease cell viability, modify cell morphology and disrupt mitochondrial membrane potential leading to abnormal expression of Bax and Bcl2 protein but had no effect on caspase-3 [142]. RSV is also found to reduce DDX5 (also known as P68) protein expression and cause cell death by inhibiting the mTORC1 pathway in prostate cancer cells [143]. The research conducted by Selvaraj discovered that RSV triggered autophagic cell death in PC3 and DU145 cells by regulation of store operated calcium entry (SOCE) machinery in addition to downregulation of stromal interaction molecule 1 (STIM1) expression and induction of ER stress by decreasing ER calcium pool [144]. Dhar revealed that RSV downregulated metastasis associated protein 1 (MTA1), a PTEN inhibitor thereby causing inhibition of AKT pathway and hence controlling prostate cancer progression [145]. In LNCaP-FGC cells, when RSV treatment showed the inhibition of IL-6/DHT (Interleukin-6/dihydrotestosterone) induced androgen receptor (AR) transcriptional activity and partly mediated through suppression of STAT-3 reporter gene activity to hinder prostate cancer [146]. RSV along with other wine polyphenols showed anti-proliferative effects and induction of apoptosis in LNCaP cells via reduced expression of androgen receptor (AR) and caspase -3-7 [147]. Fang showed that RSV increased the sensitivity of melanoma cells to radiation by suppressing proliferation and inducing apoptosis [148]. Another study demonstrated that RSV inhibited cancer cell growth by upregulation of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) expression and enzymatic activity which results in mitochondrial accumulation of H<sub>2</sub>O<sub>2</sub> to finally induce apoptosis [149]. In an investigation, RSV was found to possess a cytotoxic role in a dose and time dependent manner in prostate carcinoma (CWR22) cells *in vitro* but no effect in the *in vivo* study [150]. In addition, RSV when used in combination with radiation therapy resulted to enhanced anti-proliferative effect through upregulation of p15, p21 and p53 and downregulation of cyclinB, cyclinD and cdk2 [151]. Moreover, a study by Rashid A suggested that RSV causes cell cycle arrest, induces apoptosis and enhances the sensitivity of prostate cancer cells to ionizing radiation by modulating AMPK, Akt and mTOR signaling pathway [152]. Harada discovered that RSV inhibited DNA binding of androgen receptor (AR), by decreasing the level of acetylation of AR and hence reducing the prostate cancer development [153]. An investigation performed on prostate cancer by Chakraborty found that pterostilbene was able to suppress the cell growth factors like Akt, Bcl-2 and induce the mitochondrial apoptotic signals like Bax and caspases, and also inhibit MMP-9 and AMACR which are two metastasis markers [154,155]. A comparative study among RSV and its various analog compounds concluded that trans-RSV trimethyl ether was the most potent compound to treat prostate cancer (LNCaP) cells via cell cycle arrest and apoptosis [155]. Shi demonstrated that RSV suppressed AR gene expression via inhibition of AR-transcriptional activity [156]. Additional studies conducted by Kai confirmed that RSV downregulated MTA1 expression which destabilized the MTA1/NuRD complex which caused decrease in activation of P53 ultimately resulting to decrease in cell growth and activation of pro-apoptotic genes in prostate cancer cells [157]. RSV inhibited proliferation of AR-positive hormone non-responsive (CWR22Rv1) cells along with reduction of expression of NF-kappaB p65 via signaling pathway involving NQO2 protein [158]. Gill discovered that RSV could sensitize androgen independent prostate cancer cells to apoptosis through multiple mechanisms such as Akt, Bax, IAPs in PC-3 cells and DU145 cells [159]. Study of TRAIL-resistant LNCaP cells showed that RSV upregulated Bax, Bak, PUMA, NOXA, Bim and downregulated Bcl-2, Bcl-xL, XIAP and surviving and

sensitized the cells along with activation of caspase-3 and caspase-9 which triggered apoptosis [160]. In a study of transgenic adenocarcinoma mouse prostate males, the dietary RSV fed to the mouse revealed significantly decrease in cell proliferation, increase in androgen receptor, estrogen receptor-beta and insulin-like growth factor-1 receptor and insulin-like growth factor (IGF)-1 suggesting the suppression of prostate cancer development [161]. A study by Benitez DA showed that RSV have anticancer property in both androgen-sensitive and androgen-non-sensitive human prostate tumors by inhibiting PI3K signaling pathway [162]. Another study suggested that RSV caused sensitization of human prostate cancer (DU145) cells to ionizing radiation and accumulation of ceramide which is a potential mediator of anti-cancer activity induced by RSV [163]. Aziz showed in their study that RSV caused suppression of PI3/AKT which caused modulation of Bcl-2 family protein to induce apoptosis of LNCaP cells [164]. A study on an androgen-resistant human prostate cancer (DU145) cells revealed that RSV and propolis extract when treated caused cell death via necrosis and apoptosis respectively suggesting these micronutrient as an alternative to chemotherapy [165]. Gao in their *in vivo* and *in vitro* research showed that RSV and genestein modulated AR function for chemopreventive effect via activation of Raf-MEK-ERK kinase pathway [166]. Another investigation on prostate cancer cells found that RSV inhibited the proliferation of DU145 cells with a normal apoptotic mechanism besides suppressing the expression of heat shock proteins (HSPs70) [167]. In a research conducted by Kim found that RSV when treated to human prostate cancer (DU145) cells resulted to cell growth inhibition and apoptosis in a dose-dependent manner via activation of caspase-3 and caspase-9 [168]. A genetic analysis of LNCaP cells showed that RSV induced genes related to prostate cancer such as prostate specific antigen, AR co-activator ARA24 and NF-kappaB p65 which are associated with activation of p53 responsive genes- p53, p21, p300/CBP and Apaf-1 [169]. Ding found that RSV inhibited cell growth by inducing cell cycle arrest at sub-G0/G1 cells and apoptosis in PANC-1 and AsPC-1 cells [170]. Similarly, Morris found that RSV inhibited cell growth by inducing apoptosis in independent of the hormone responsive or unresponsive LNCaP cells [171]. Another study on LNCaP cells showed that RSV inhibited the proliferation of the cells by arresting cell cycle at S phase and by inhibiting DNA synthesis [172]. Additionally, RSV was found to suppress prostate specific antigen, human glandular kallikrein-2, AR-specific coactivator ARA70 and the CDK inhibitor p21 showing RSV as a potent therapeutic agent for prostate cancer [173]. A study by Hsieh TC reported that RSV caused apoptosis of LNCaP and lowered prostate-specific antigen (PSA) levels which demonstrated the anticancer role of RSV against prostate cancer [174].

### Resveratrol and pancreatic cancer

Pancreatic cancer is a fatal disease with a very poor prognosis with low survival rate due to late stage diagnosis of the cancer as most of the pancreatic cancer patients are asymptomatic until advanced stage of the disease [175]. A study showed that RSV suppressed the development of ROS-induced pancreatic cancer by inhibiting hedgehog signaling proteins, which also suppressed the levels of uPA and MMP2 proteins [176]. RSV induced apoptosis in capan 2 and colo 317 cells by activating caspase 3 and upregulated the protein expression of P53 and P21 in pancreatic cancer cells [177]. Li showed that RSV not only inhibited cell growth, migration, and invasion, but also helped in the expression of EMT-related genes for metastasis through inhibition of the PI3/Akt/NF-kB signaling pathway [178]. Another research revealed that different pancreatic cancer cells, such as PANC-1, BXPC-3, and ASPC-1, had different responses to RSV-induced apoptotic cell death

by regulating the expression of caspases, Bcl-2, Bcl-xL, XIAP, and Bax [179]. RSV treatment of human pancreatic cancer stem cells in Kras (G12D) mice inhibited growth and development of pancreatic cancer, caspase-dependent apoptosis, and inhibition of migration, invasion, and EMT [180]. RSV suppressed ROS-induced pancreatic cancer progression by inhibiting the ERK and P38 MAPK signaling pathways [181]. Furthermore, pterostilbene, a derivative of RSV, inhibited *in vitro* cell proliferation by caspase activation, mitochondrial membrane depolarization, and cell cycle arrest in pancreatic cancer [182]. Zhu found that RSV when treated in combination with Metformin caused upregulation of Bax, cleaved-caspase3 and downregulation of Bcl-2 showed anti-cancer property in pancreatic cancer (Paca) cells [183]. A study found that RSV inhibited cell growth and activated apoptosis by activation of AMPK and increased sensitivity to gemcitabine by inhibiting YAP expression in pancreatic cancer cells [184]. In another study, RSV in combination with apocynin inhibited cell proliferation and arrested cell cycle progression at G1 phase with cyclin D1 downregulation and inactivation of Akt-GSk3beta and ERK1/2 in a human and hamster pancreatic cancer cells [185]. Study of MIA PaCa-2 cells showed that RSV inhibited cell proliferation and colony formation by inducing apoptosis of MIA PaCa-2 cells along with the decreased level of Ihh, Ptch and Smo suggesting the inhibition of Hedgehog signaling pathway [186]. In pancreatic cancer capan-2 cells, Yang discovered that RSV acted as a tumor inhibitor via upregulation of Bax, however, it also induced tumorigenesis by upregulating VEGF-B, and hence, combinatorial effect of RSV and inhibitor of VEGF-B might be a favorable strategy for treatment of pancreatic cancer [187]. RSV inhibited the cell viability of pancreatic cancer cells by inhibiting miR-21 which subsequently inhibited Bcl-2 expression resulting to apoptosis [188]. In an investigation, RSV inhibited cell growth via induction of apoptosis through downregulation of downstream target proteins of Hedgehog pathway such as Gli1, Ptc1, CCND1 and BCL-2 in pancreatic cancer PANC-1 cells [189]. Roy showed that when RSV was treated to pancreatic cancer cells, upregulation of p21/CIP1, p27/kip1 and inhibition of cyclinD1 caused cell cycle arrest while activation of caspase-3 triggered apoptosis through inhibition of FOXO transcriptional activity dependent upon ERK and AKT pathway [190]. In a study, RSV induced apoptosis including cell cycle arrest at S and G0/G1 phase through downregulation of AKT signaling in insulinoma INS-1E cells [191]. Golkar reported that when RSV is treated to pancreatic cells, it showed a significant decrease in cell proliferation through upregulation of Macrophage inhibitory cytokine (MIC-1) gene indicating its key role in RSV induced anti-cancer property [192].

### Resveratrol and lung cancer

Lung cancer is the most common cancer and a leading cause of cancer-associated mortality worldwide. The risk factors for lung cancer include cigarette smoking; indoor air pollution; chemicals such as polycyclic aromatic hydrocarbons; genetic factors such as chromosome abnormalities, mutations, and structural hydrocarbons; and disease-associated factors such as chronic obstructive pulmonary disease and chronic bronchitis [193]. RSV has been reported to augment etoposide-induced cytotoxicity in human non-small cell lung cancer (NSCLC) cells by downregulating ERK1/2- and AKT-mediated expression of the X-ray Repair Cross-Complement Group-1 protein [194]. A similar study on NSCLC showed that RSV enhanced the anticancer effect of cisplatin by inducing cell apoptosis and mitochondrial dysfunction [195]. RSV has been proven to inhibit transforming growth factor (TGF)- $\beta$ 1-induced EMT, which is known to promote invasion and metastasis of carcinoma [196]. A RSV analog 3,44'-trihydroxy-trans-stilbene (10-80  $\mu$ mol/L) inhibited cell viability of NSCLC, A549 cells,

by inducing apoptosis, increasing acidic compartments in cells and LC3-II accumulation and GFP-LC3 labelled autophagosomes in the cells, also, the cell death accentuated when autophagy was inhibited by an autophagy inhibitors such as 3-methyladenine and wortmannin. In addition, it also elevated reactive oxygen species [197]. RSV treatment sensitized NSCLC cells to radiotherapy by increasing ROS production and ionizing radiation-induced premature senescence [198].

### Resveratrol and brain tumors

Glioblastoma is the most morbid form of brain tumor in adults and has poor prognosis [199]. Lin showed that RSV strongly inhibited cell growth and induced apoptosis in A172 and T98G glioblastoma cells by activating Notch-1 and restoring wild-type P53 expression in a time- and dose-dependent manner [200]. Another study indicated RSV as a potential anti-tumor agent for glioblastoma multiforme CD133+ cells, *in vivo* and *in vitro*, by inhibiting the self-proliferating capacity of the brain tumor, decreasing the invasion ability, and enhancing apoptosis by radiotherapy through suppression of the STAT3 pathway [201]. Glioblastoma-initiating cells play significant roles in the onset, growth, and recurrence of glioblastoma multiforme. Although glioblastoma is highly resistant to temozolomide, addition of RSV enhanced the sensitivity of these glioblastoma-initiating cells to temozolomide and induced apoptosis through double-stranded DNA breaks, including an increase in differentiation of glioblastoma-initiating cells, through STAT3 inactivation [202]. Further research has demonstrated that RSV inhibited cell proliferation, arrested the S-phase cell cycle, and induced apoptosis *in vitro*; it suppressed intracranial C6 tumor growth *in vivo* by significantly downregulating oncomiRs (miR21, miR30a-5p, and miR19) that target the p53, PTEN, EGFR, STAT3, COX-2, NF- $\kappa$ B, and PI3/Akt/mTOR pathways [203]. An investigation by color Doppler ultrasound showed that RSV suppression of glioma growth was significantly dependent on the inhibition of macroscopic and microscopic angiogenesis [204]. Zhang confirmed the YKL-40 gene as the most overexpressed gene in glioblastoma; RSV treatment suppressed YKL-40 expression *in vitro* and reduced the phosphorylation of ERK1/2 in a time-dependent manner [205]. A study on c-Myc expression in medulloblastoma cells found that c-Myc downregulation by RSV was an important cause of suppression of medulloblastoma activity through growth inhibition, cell cycle arrest, and apoptosis of medulloblastoma tissues and cell lines (UW 229-2 and UW 228-3) [206]. A recent study revealed that RSV was able to suppress cell proliferation, increase cell death and decrease cell motility by regulating WNT signaling pathway and EMT activators in Glioma Stem Cells [207]. In a study of rat glioblastoma, RSV administered through lumbar puncture was found to significantly inhibit rat glioblastoma development via inactivation of STAT3 signaling pathway and by promoting autophagy and apoptosis [208]. Clark found that RSV inhibited cell growth, invasion of U87 glioma and glioma stem-like cell and also suppressed glioblastoma xenograft growth by reducing AKT phosphorylation and by inducing P53 expression [209]. A study on by Ryu demonstrated that RSV induced apoptosis and inhibited cell growth by increasing the expression of tristetraprolin in human glioma (U87MG) cells [210]. In another study of human glioma cells, Yang discovered that RSV effectively inhibited the expression of pokémon to enhance cell apoptosis, senescence and antiproliferation induced by RSV [211]. A study on glioma stem cells (GSCs), RSV was found to reduce self-renewal and tumor-initiating ability of GSCs by inhibiting Nanog via activating P53/P21 pathway [212]. Study of glioma (C6) cells by Figueiro showed that nanocapsulation of RSV enhanced the therapeutic action of RSV *in vitro* as well as *in vivo* by initiating cell cycle arrest and apoptosis compared to normal solution of RS. Research by Wang C



reported that RSV inhibited proliferation of GH3 cells by inducing G0/G1 cell cycle arrest and apoptosis and decreasing prolactin production [213]. Lin CJ found that combination of RSV and temozolomide caused decrease of growth of tumor by suppressing ROS/ERK-mediated autophagy and apoptosis in glioma cells [214]. In an *in vitro* and *in vivo* investigation, RSV was found to induce senescence of glioma cells and caused cell growth inhibition by suppressing mono-ubiquitination of histone H2B at K120 (uH2B) [215]. In a study of U87MG cells, RSV was able to suppress the growth of malignant glioblastoma by inhibiting expression of nestin but by increasing expression of glial acidic fibrillary and betaIII-tubulin in time dependent manner [216]. Another study showed that RSV induced cell cycle arrest at S phase with an increase in histone H2AX phosphorylation in human glioblastoma cells by inhibiting recombinant human TOPO II alpha to decatenate kDNA which act as TOPO II poison [217]. Li revealed that RSV induced autophagy in human U251 glioma cells and autophagy played protective role and hence concluded that autophagy inhibitor can increase the efficacy of RSV to suppress the proliferation of glioma cells [218]. A study of CD133+ cells derived from teratoid/rhabdoid tumor revealed that RSV inhibited cell proliferation, induced apoptosis and increased radiosensitivity as a therapeutic effect to the brain tumor [219]. Additionally, RSV initiated neuronal differentiation of medulloblastoma cells and suppressed expression and phosphorylation of STAT3 along with its downstream genes such as survivin, cyclinD1, COX-2 and c-Myc and in UW228-2 and UW228-3 cells [220].

### Resveratrol and breast cancer

Although breast cancer has a decreasing incidence, it remains the second leading cause of cancer deaths in women in the US [221]. The treatment strategies available for breast cancer are chemotherapy, radiation, and surgical resection of tumors; hormonal therapy may also be given for post-menopausal women [222]. Khan showed that RSV treatment induced breast cancer cell apoptosis by downregulating FASN and HER2 genes synergistically. Additionally, RSV attenuated PI3K/Akt/mTOR pathway signaling by downregulating Akt-phosphorylation and upregulating PTEN expression [223]. RSV treatment reduced the expression of  $\beta$ -catenin and cyclin-D1 *in vitro* and *in vivo* [224]. Another study showed that RSV significantly enhanced doxorubicin-induced death of multidrug-resistant breast cancer cells *in vitro* and decreased 60% of the tumor volume under similar *in vivo* conditions [225]. Rsv or triacetyl-Rsv induced cell cycle arrest and apoptosis and initiated P53 activation in MCF-7 and MDA-MB231 breast cancer cells to control the cancer cell proliferation [226]. In an experimental rat model of mammary tumor, Chatterjee showed that daily dietary supplement of 0.001% RSV for 24 weeks increased apoptosis and decreased DNA damage, cell growth, and levels of 5-lipoxygenase, TGF- $\beta$ 1, and NF- $\kappa$ B [227].

### Resveratrol and skin cancer

RSV has been shown to initiate senescence in human A431 squamous cell carcinoma cells by blockade of its autolysosome form and downregulation of Rictor protein expression, resulting in alteration of cytoskeleton and suppression of skin cancer progression [228]. A study on a mouse model of skin tumor concluded that RSV regulated apoptosis and cell survival by upregulating P53 and Bax, downregulating BCL-2 and surviving expressions, and regulating the PI3K/AKT pathway [229]. An *in vitro* and an *in vivo* study of skin cancer revealed that the synergistic effect of RSV and 5-FU caused cell cycle arrest of TE-1 and A431 cancer cells at S-phase, as well as apoptosis with increased protein levels of p53, cleaved caspase-3, cleaved PARP,

and Bax/Bcl-2 ratio [230]. Moreover, topical application of RSV (25  $\mu$ M) on the skin significantly reduced tumorigenesis in the mice [231]. Kim demonstrated that oral administration of RSV significantly suppressed ultraviolet-induced skin tumorigenesis in p53 (+/-)/SKH-1 mice that were highly tumor-susceptible through an Akt-mediated downregulation of TGF- $\beta$ 2 [232]. RSV suppressed the development of human skin squamous cell carcinoma A431 cells in nude mice through a caspase-3-dependent apoptotic pathway and by downregulation of protein expression of surviving [233]. After multiple exposures of SKH-1 nude mice model to ultraviolet B, RSV was topically applied on the skin; immunoblot and immunohistochemical analysis revealed that the anti-proliferative property of RSV was mediated through the modulation of important cell cycle regulatory proteins, probably through inhibition of the MAPK pathway. RSV decreased the viability of immortalized human keratinocytes by dephosphorylation of Akt and phosphorylation of ERK1/2, which is linked to the induction of p66Shc-Ser36 phosphorylation [234].

### Resveratrol and leukemia

Chronic myelogenous leukemia (CML) is a cancer of the white blood cells that occurs due to a reciprocal translocation between chromosomes 9 and 22 [235]. Wu discovered that treatment with RSV (20–100  $\mu$ M) induced apoptosis and phosphorylation of histone H2AX in CML K562 cells through regulation of P38 and JNK, which are associated with the MAPK pathway [236]. When acute lymphoblastic leukemia (ALL) CCRF-CEM cells were treated with RSV, there was dose-dependent cell death along with upregulation of miR16-1 and miR15a expressions, as analyzed by real-time polymerase chain reaction [237]. A study concluded that RSV inhibited proliferation of T-cell ALL cells by inducing cell cycle arrest, apoptosis, and autophagy through suppression of the Akt/mTOR/p70s6k/4E-BP1 pathway and activation of the P38-MAPK signaling pathway [238]. Human CML K562 cells treated with imatinib mesylate in combination with RSV were shown to have a significant decrease in cell viability and increased apoptosis, compared to the treatment with imatinib mesylate alone [239]. In a study, hydroxylated RSV analogs were reported to induce cell death, accompanied by loss of mitochondrial potential, oxidative stress, loss of superoxide dismutase activity, and increased activity of caspase-3 and caspase-9 [240]. Yaseen showed that RSV in combination with histone deacetylase inhibitors induced cell death through generation of ROS, activation of an extrinsic apoptotic pathway, and induction of DNA damage, including upregulation of death receptor-5 [241]. Furthermore, RSV combined with arsenic trioxide induced apoptosis, mitochondrial damage, and oxidative stress in acute promyelocytic leukemia; RSV also prevented cardiotoxicity caused by arsenic trioxide [242].

### Harmful effects/side-effects of Resveratrol

There are numerous studies that indicated RSV as an anticancer therapeutic agent, but some studies have mentioned the negative effects of RSV. RSV has been reported to downregulate PTEN-mRNA expression and upregulate BCL-xL mRNA expression, causing proliferation and survival of liver cancer HepG2 cells [243]. Another study stated that after oral administration to the animal models, RSV accumulated in various internal organs, especially in the heart, liver, kidneys, and stomach [131]. Another limitation of RSV is its poor bioavailability, which precludes its significant healing functions [244]. A trial suggested that by regulating circulatory function in the brain, RSV could improve mood and cognition and reduce the possibility of dementia in post-menopausal women and in other populations at risk

[245]. RSV has been shown to have beneficial effects in high-fat diet and obesity; however, it increased the expression of fasting-induced adipogenic factor in the intestines of mice fed a high-fat diet and accelerated the progression of obesity [246]. Roberts found that RSV use in pregnancy caused an unexplained variation in fetal pancreatic development; this study warned about RSV administration to pregnant women [247]. In a study of eight healthy subjects who received 2 g RSV twice per day for eight days, six suffered mild episodic diarrhea and one developed rash and headache [248]. In long-term studies of 24 months in rats and 18 months in mice, chronic exposure to RSV at a daily dose of less than 1g/kg had no adverse effects (7); on the other hand, oral intake of more than 3 g/kg per day resulted in neuropathy, renal toxicity, and liver toxicity in a group of rats [249,250].

### Clinical trials on Resveratrol

The first clinical trial on the effect of RSV in eight patients with colon cancer demonstrated that low-dose RSV inhibited WNT signaling in normal colonic mucosa, indicating its beneficial role in colon cancer prevention [89]. A clinical trial on middle-aged men with metabolic syndrome showed that the daily intake of high-dose RSV (1000 mg) for four months decreased the serum levels of androgen precursors, but there were no changes in prostate size, PSA level, and testosterone level; these suggested that RSV has no beneficial effects in prostate cancer [251]. In a study involving six patients with liver cancer, three patients consumed placebo and another three consumed RSV (5000 mg/day) for 10–21 days before surgery. In RSV-administered patients, RSV was detected in hepatic tissues and the apoptotic marker cleaved-caspase-3 increased by 39%; however, no effect was observed in well-known markers of cancer, such as Akt, ERK, beta-catenin, JNK, surviving, or BCL-2 [90]. Another study revealed that 12-week supplementation with 500 mg RSV reduced ALT and hepatic steatosis in patients with NAFLD, but there was no effect on blood pressure, insulin resistance markers, and lipid profile [252]. In 119 participants who were randomly given oral placebo or RSV 500 mg daily for 52 weeks, RSV was observed to penetrate the blood-brain barrier and was measurable in plasma and CSF; the adverse effects were nausea, diarrhea, and weight loss [253]. A clinical trial of two weeks of high-dose RSV reduced intestinal and hepatic lipoprotein production; however, long-term studies are required to verify the potential clinical benefits of RSV in patients with increased level of triglyceride-rich lipoproteins [254]. A randomized, double-blind, placebo-controlled, parallel-group study on 60 adults aged 18–30 years showed that single-dose RSV intake for 28 days significantly decreased the subjective ratings of fatigue [255].

### Conclusion

Various studies have shown that RSV has promising therapeutic effects on different cancers (Figures 1-3). Increasing number of studies on RSV provides insights into the molecular pathways and mechanisms of action of the RSV on cancer. In this review, we summarize the recent studies of RSV on the molecular mechanisms and pathways of actions against major cancers (Table 1) RSV inhibited cell cycle regulation, invasion/metastasis, angiogenesis and induced apoptosis and autophagy mediated through the regulated cell cycle-associated proteins; induced BCL-2/BAX and AMPK; inhibited the PI3K/Akt/Mtor, WNT, MEK, ERK pathways. However, the side-effects or harmful effects of RSV should be considered before administration. Only few human clinical trials have shown beneficial effects of RSV in diseases, but several have shown a neutral effect, probably due to its low bioavailability. Therefore, further active experimental research on RSV can give us a deeper understanding of its therapeutic effects on cancer.

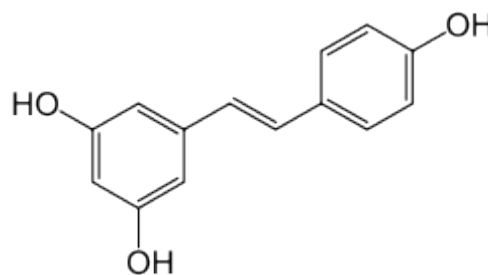


Figure 1: Molecular structure of resveratrol.

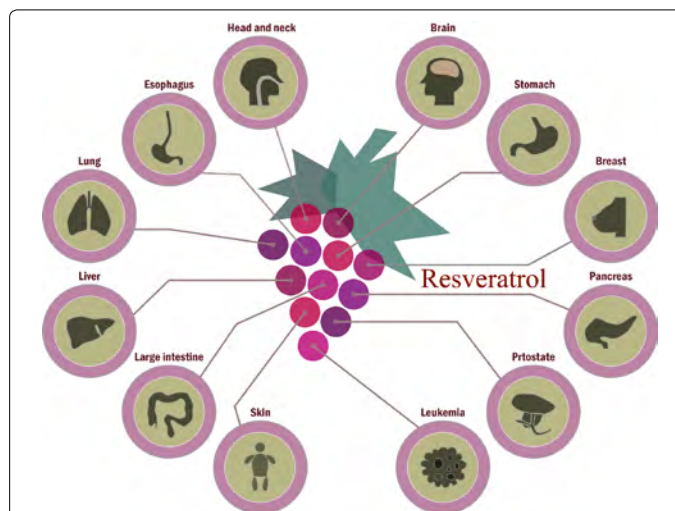


Figure 2: Schematic picture of therapeutic roles of resveratrol in various human cancers.

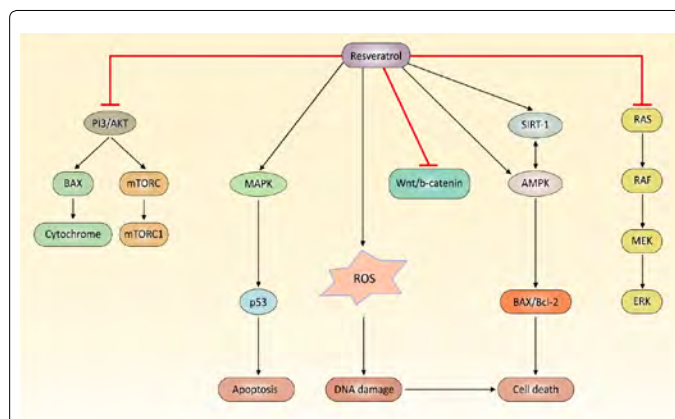


Figure 3: Various therapeutic effects of resveratrol. Multiple signaling pathways associated with human cancers including head and neck, esophageal, gastric, colorectal, liver, prostate, pancreatic, lung, brain, breast, skin, and leukemia cancers are regulated by resveratrol in the process of apoptosis, DNA damage, cell death, Wnt, Erk, and Akt signaling pathway. Black arrows indicate activation cascade, while red lines indicate the inhibition cascade by resveratrol.



Cancer	Effect of Resveratrol	References
	Inhibition of STAT3, cell cycle	[27,29,33,35]
<b>Head and neck cancer</b>	Activation of AMPK, apoptosis	[28,30,32,38,42,44,45]
	Regenerating gene expression	[39]
	JNK1/2 and ERK1/2 signaling	
	ER stress, autophagy	[37,43]
	Inhibition of migration/ invasion	[36,40]
	DNA damage/Smad 4 signaling	[41]
	Cell cycle arrest at G1-phase	[46,47]
<b>Esophageal cancer</b>	Increase apoptosis	[32]
	Inhibition of COXs and PG (E2)	[48]
	Inhibition of BCL-2 and increase in BAX	[49]
	Inhibition of P27kip1(CDK inhibitor)	[50]
	Chemopreventive effect	[51,52]
	Cell cycle arrest at G1-phase	[59,61,67,71]
<b>Gastric cancer</b>	Antioxidant action, autophagy, metabolism	[62,63,65,70]
	Induction of apoptosis	[57,66,68,69]
	Inhibition of migration/invasion	[58,60]
	Inhibition of NF-κB and EMT	[74]
	Activation apoptosis	[75,82,87]
<b>Colorectal cancer</b>	Inhibition of invasion/metastasis	[76,80,81,91]
	Activation of ER-stress and apoptosis	[77,89,90,98-101,103,104]
	Cell cycle arrest and cyclin-D1/CDK4 complex	[78,83,85,86,92-94,105]
	Sirt1 and p38 MAPK signaling pathway	[79,84]
	Wnt/beta catenin signaling pathway	[95,96]
	Induce Autophagy	[97]
	Downregulation of telomerase activity	[102]
	Inhibition of cyclin-D1, MAPK, and cell cycle	[108,109,110,113,124,125]
<b>Liver cancer</b>	Inhibition of STAT3 and Akt	[111]
	Inhibition of angiogenesis/metastasis	[112,116,120,121,123,127]
	Inhibition of invasion	[128,129,133]
	Increase apoptosis	[114,115,119,126,130,131]
	Inhibition of Met signaling	[132,134]
	Inhibition mTOR and ERK	[116-118]
	Decrease COX-2 and NFκB	[122]
	Inhibition of AKT/EMT	[136,137,164]
	Inhibition of AKT/EMT	[136,137,164]
<b>Prostate cancer</b>	Inhibition of beta-catenin/HIF1-α	[138]
	Inhibition of metastasis/angiogenesis	[139,144,145,154]
	Inhibition of NF-κB and PI3K/ apoptosis	[140,142,149,155,157,159]
	Induce apoptosis	[160,167,168,171,173]
	Cell cycle arrest	[141,150,151,152,170,172]
	mTORC inhibition	[143]
	Autophagy	[144]
	Reduce androgen receptor	[147,148,153,156,158,161]
	Modulate androgen receptor function	[162,165,166,169,174]
	Accumulation of ceramide	[163]
	Inhibition of uPA and MMP2, invasion	[176]
<b>Pancreatic cancer</b>	Increase P53 and P21, cell cycle arrest	[182,185,190,191]
	Inhibition of PI3K/Akt/NF-κB	[68]
	Inhibition of BCL-2 and increase in BAX	[179,183]
	Inhibition of P38 and MAPK	[181]
	Inhibition of Hedgehog signaling pathway	[186,189]
	Reduced angiogenesis	[187]
	Inhibition of ERK1/2	[194]
<b>Lung cancer</b>	Increase apoptosis and mitochondrial dysfunction	[195]
	Inhibition of invasion/metastasis	[196]
	Increase ROS and autophagy	[197,198]
	Induction of apoptosis	[16,200,210,211,214,219]
	Inhibition of STAT3 and invasion	[201,202]
	Cell cycle arrest at S-phase	[203,206,211,213,217]

<b>Brain cancer</b>	Inhibition of angiogenesis and invasion/metastasis	[204,209]
	Inhibition of YKL-40 and ERK1/2	[205]
	Inhibition of WNT signaling and EMT	[207]
	Inactivation of STAT3 signaling pathway/ autophagy	[208,218,220]
<b>Breast cancer</b>	Inhibition of Nanog via activation of p53/p21	[212]
	Suppressed histone H2B at K120 and nestin	[215,216]
	Downregulation of PI3K/Akt/Mtor	[223]
	Reduced beta catenin and cyclin D1	[224]
	Cell cycle arrest	[226]
	Decreased DNA damage	[227]
	Inhibition of Rictor	[228]
	Upregulation of P53 and Bax/ apoptosis	[229,230,233]
<b>Skin cancer</b>	Reduced tumorigenesis	[231]
	Inactivation of AKT and Erk1/2	[232,234]
	Cell cycle arrest by inhibition of MAPK pathway	[10]
	Induction of apoptosis	[236,239,240]
<b>Leukemia</b>	Upregulation of miR16-1 and miR15a	[237]
	Activation of P38/MAPK	[238]
	DNA damage, ROS activation	[241,242]

**Table 1:** Summary of the therapeutic effects of resveratrol in various cancers.

## Conflict of Interest

No potential conflicts of interest relevant to this article are reported.

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