Disease-associated regulation of gene expression by resveratrol: Special focus on the PI3K/AKT signaling pathway

Soudeh Ghafouri-Fard1, Zahra Bahroudi2, Hamed Shoorei3, Bashdar Mahmoud Hussen4,5, Seyyedeh Fahimeh Talebi6, Sadia Ghausia Baig7, Mohammad Taheri8,9* and Seyed Abdulmajid Ayatollahi10*

Abstract

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural phenol that is present in the skin of the grape, blueberry, raspberry, mulberry, and peanut. This substance is synthesized in these plants following injury or exposure to pathogens. Resveratrol is used as a dietary supplement for a long time and its effects have been assessed in animal models of human disorders. It has potential beneficial effects in diverse pathological conditions such as diabetes mellitus, obesity, hypertension, neoplastic conditions, Alzheimer's disease, and cardiovascular disorders. Notably, resveratrol has been found to affect the expression of several genes including cytokine coding genes, caspases, matrix metalloproteinases, adhesion molecules, and growth factors. Moreover, it can modulate the activity of several signaling pathways such as PI3K/AKT, Wnt, NF-κB, and Notch pathways. In the current review, we summarize the results of studies that reported modulatory effects of resveratrol on the expression of genes and the activity of signaling pathways. We explain these results in two distinct sections of non-neoplastic and neoplastic conditions.

Keywords: Resveratrol, Gene expression, PI3K/AKT pathway, NF-κB, Notch

Introduction

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural phenol that is synthesized by numerous plants following injury or exposure to pathogens [1]. The skin of the grape, blueberry, raspberry, mulberry, and peanut is regarded as a source of resveratrol [2]. Resveratrol is used as a dietary supplement and its effects have been assessed in animal models of human disorders (Fig. 1). Resveratrol is a pan-assay interference agent that makes positive impacts in various laboratory tests [3]. These effects are mediated through its interactions with biomolecules on cell membranes [4]. In plants, resveratrol is synthesized by the enzyme resveratrol synthase [5].

In humans, resveratrol can be administered through buccal delivery being absorbed via the saliva. Yet, buccal delivery is not an efficient route since it has low aqueous solubility [6]. Moreover, high amounts of hepatic glucuronidation and sulfonation further limit the bioavailability of resveratrol [7]. Resveratrol is glucuronidated and sulfonated in the intestinal and hepatic tissues. Its sulfonation in the intestine is induced by microbial activity [8]. While the half-life of resveratrol is about 8–14 min, sulphate and glucuronide resveratrol metabolites have half-lives of more than 9 h [9].

This agent has been found to alter the expression of several genes in different pathological conditions. In the current review, we summarize the results of studies that reported modulatory effects of resveratrol on the expression of genes and the activity of signaling pathways. We...
explain these results in two distinct sections of non-neoplastic and neoplastic conditions. The main focus of this manuscript is on studies that reported modulatory effects of resveratrol on PI3K/AKT signaling pathway.

**Effects of resveratrol on gene expression in non-neoplastic conditions**

**Cardiac diseases**

In order to assess the protective effects of resveratrol against cardiac hypertrophy, Guan et al. have exposed male rats to chronic intermittent hypoxia (CIH). CIH has resulted in the elevation of heart weight/body weight and left ventricle weight/body weight ratios as well as left ventricular remodeling. Moreover, authors have reported elevation of the apoptosis index, up-regulation of oxidative biomarkers, increase in autophagy marker Beclin-1, and down-regulation of p62 in the CIH group. Intragastic administration of resveratrol has enhanced cardiac function, amended cardiac hypertrophy, and reversed CIH-induced changes in oxidative stress and apoptosis. Mechanistically, PI3K/AKT-associated suppression of the mTOR pathway has been identified as the mediator of effects of resveratrol autophagy activation following CIH stimulation [14]. In an experiment in aged rats, Lin et al. have shown swimming exercise training, resveratrol treatment, or a combination of both can improve heart function. Authors have also reported a slight increase in the activity of the PI3K/AKT pathway in rats subjected to exercise training and resveratrol treatment. Yet, the activity of SIRT1 in the aged rat hearts has been only with resveratrol treatment. Besides, rats exposed to both interventions exhibited activation of both SIRT1 and PI3K/AKT pathways and inhibition of FOXO3 accumulation [15]. Table 1 describes the impact of resveratrol on the expression of genes in the context of cardiovascular disorders.

Based on the anti-thrombotic and anti-inflammatory effects of resveratrol, this agent is also suggested to decreases COVID-19-associated mortality, which is due to activation of thrombotic and inflammatory cascades [18].

---

### Table 1  Impact of resveratrol on the expression of genes in the context of cardiovascular disorders

| Type of disease               | Dose range | Cell line | Target                              | Pathway                      | Function                                                                 | Refs. |
|------------------------------|------------|-----------|-------------------------------------|------------------------------|--------------------------------------------------------------------------|-------|
| In vivo studies              |            |           |                                     |                              |                                                                          |       |
| Cardiac Hypertrophy          | 30 mg/kg   | –         | Bax, Bcl-2, Beclin-1, p62           | PI3K/AKT/mTOR                 | RVT by targeting the PI3K/ AKT/mTOR pathway could prevent chronic intermittent hypoxia-induced cardiac hypertrophy | [14]  |
| Cardiovascular Diseases      | 15 mg/kg   | –         | SIRT1, FOXO3, Fas, FADD, Caspase-3/8, Sirt-1, BNP, TNF-α, PARP | PI3K/AKT                      | RVT via synergetic activation of PI3K/AKT and SIRT1signaling could improve the beneficial effects of exercise training in aging rat hearts | [15]  |
| Heart Failure (HF)           | 2.5 mg/kg  | –         | Caspase-3, Serca2a, PLB             | PI3K/AKT/eNOS                 | RVT via the PI3K/AKT/eNOS pathway could decrease reduces atrial fibrillation susceptibility in HF | [16]  |
| In vitro studies             |            |           |                                     |                              |                                                                          |       |
| Acute Myocardial Infarction  | 20 μM      | Cardiomyocyte | –                                 | PI3K/AKT/e-NOS                 | RVT via blocking the PI3K/AKT/e-NOS pathway could protect cardiomyocyte apoptosis induced by I/R injury in AMI | [17]  |
Central nervous system (CNS) disorders
Resveratrol has been found to have neuroprotective effects against early brain injury (EBI) following subarachnoid hemorrhage (SAH). Experiments in rat models have shown that intraperitoneal administration of this agent decreases mortality and brain edema following SAH. Moreover, resveratrol has enhanced neurological scores in these animals. Histological studies have shown the effect of resveratrol in the reduction of neuronal pyknosis and swelling. Moreover, resveratrol has enhanced expressions of beclin-1, LC3-II, LC3-II/LC3-I, and Bcl-2, while decreasing p-AKT, p-mTOR, p62, cleaved caspase-3, caspase-9, and BAX levels. Further studies have verified the effects of resveratrol in the induction of autophagy. Therefore, the neuroprotective effect of resveratrol is exerted through the regulation of autophagy and apoptosis via modulating the AKT/mTOR pathway [19].

Neuroprotective effects of resveratrol have also been investigated in a rat model of middle cerebral artery occlusion. Resveratrol has remarkably enhanced neurological function, decreased cerebral infarct size, reduced neuron injury, and diminished neuron apoptosis. Mechanistically, resveratrol up-regulates p-JAK2, p-STAT3, p-AKT, p-mTOR, and BCL-2 levels, while down-regulating cleaved caspase-3 and BAX levels. Taken together, resveratrol protects against cerebral ischemia/reperfusion injury through induction of the activities of JAK2/STAT3 and PI3K/AKT/mTOR pathways [20]. Another experiment has shown that resveratrol reduces neurological deficit scores and MPO activity and suppresses induction of IL-1β, TNFα, and COX2 inflammatory markers. In addition, resveratrol attenuates ischemic brain injury following cerebral artery occlusion via modulation of PI3K/AKT signaling pathway [21] (Fig. 2). Through upregulating heme oxygenase-1 (HO-1) via the PI3K/AKT/Nrf2 axis, resveratrol can attenuate the cytotoxic effects of amyloid-β1–42 in PC12 cells [22]. Moreover, through activating PP2A and PI3K/AKT induced-inhibition of GSK-3β, resveratrol can inhibit Tau phosphorylation in the rat brain [23]. Thus, resveratrol may be considered as an anti-Alzheimer’s disease substance. Table 2 describes the impact of resveratrol on the expression of genes in the context of CNS disorders.

A clinical trial in patients with Alzheimer’s disease has shown measurable levels of resveratrol and its major metabolites in plasma and cerebrospinal fluid of patients following treatment with this substance. However, brain volume loss has been promoted by treatment with resveratrol [33].

Diabetic complications
The beneficial effects of resveratrol on cardiac function have been assessed in an animal model of diabetic cardiomyopathy. Resveratrol has suppressed high glucose-associated apoptosis of ventricular myocytes in neonatal rats. Moreover, resveratrol has reversed the effects of high glucose in reduction of cell viability, inhibition of AKT and FoxO3a phosphorylation, and suppression of cytoplasmic transfer of FoxO3a. The protective effects of resveratrol have been abolished by a PI3K inhibitor, indicating that the therapeutic effect of this agent is mediated through inhibition of apoptosis via the PI3K/AKT/FoxO3a pathway, [36]. Another study has shown that resveratrol through up-regulating mmu-miR-363-3p via the PI3K/AKT pathway can reverse high-fat diet-induced insulin resistance [37]. Resveratrol has also shown protective effects against high glucose-associated apoptosis and senescence of nucleus pulposus cells. Functionally, resveratrol inhibits the production of reactive oxygen species (ROS) and activates PI3K/AKT pathway under the high glucose condition [38]. The protective effects of resveratrol against diabetic nephropathy are exerted through modulation of PI3K/AKT/FoxO3a pathway,
Table 2: Impact of resveratrol on the expression of genes in the context of CNS disorders

| Type of disease                        | Dose range | Cell line                  | Target                              | Pathway                               | Function                                                                 | Refs. |
|----------------------------------------|------------|----------------------------|-------------------------------------|---------------------------------------|--------------------------------------------------------------------------|-------|
| **In vivo studies**                    |            |                            |                                     |                                       |                                                                          |       |
| Subarachnoid Hemorrhage (SAH)          | 60 mg/kg   | --                        | Beclin-1, LC3-II, Bcl-2, p62, Caspase-3/9 | AKT /mTOR                            | RVT via downregulating AKT/mTOR pathway could promote the autophagy process in SAH model rats | [19]  |
| Cerebral Ischemia Injury (CII)         | 30 mg/kg   | --                        | Bcl-2, Bax, Caspase-3               | JAK2/STAT3, PI3K/AKT/mTOR             | RVT via activating JAK2/STAT3/PI3K/AKT/mTOR pathway could provide neuroprotection against cerebral I/R injury | [20]  |
|                                        | 100 mg/kg  | --                        | IL-1β, TNFα, COX2                  | PI3K/AKT                              | RVT via activating PI3K/AKT pathway could attenuate brain damage in permanent focal cerebral ischemia | [21]  |
|                                        | 30 mg/kg   | --                        |                                     | AKT/GSK-3β                            | RVT via regulating the AKT/GSK-3β pathway could improve neuronal damage against MCAO-induced CII | [24]  |
|                                        | 20 mg/kg   | --                        | GSK-3β, DJ-1, PTEN, Nrf-2, Bax, Caspase-3, Bcl-2 | PI3K/AKT, PI3K/AKT                   | RVT via reducing of DJ-1 expression and activating of PI3K/AKT/GSK-3β pathway could contribute to post I/R cerebral damage | [25]  |
| Chronic cerebral hypoperfusion (CCH)   | 50 mg/kg   | --                        | Caspase-3, Bcl-2, Bax, LC3B, 4E-BP1, Beclin-1, S6K1 | PI3K/AKT/mTOR                        | RVT via the AKT/mTOR pathway could improve cognitive dysfunction in rats with CCH | [26]  |
| Alzheimer’s Disease (AD)               | 0–40 μM    | PC12                      | HO1                                 | PI3K/AKT/Nrf2                          | RVT by upregulating heme oxygenase-1 (HO-1) via the PI3K/AKT/Nrf2 axis could attenuate the cytotoxicity induced by amyloid-β1–42 in PC12 cells | [22]  |
|                                        | 300 mg/kg  | --                        | PP2A, GSK-3β, Tau, Caspase-3, Bcl2, Bax | PI3K/AKT, AMPK                        | RVT via activating PP2A and PI3K/AKT inhibited-inhibition of GSK-3β could inhibit Tau phosphorylation in rat brain | [23]  |
| Parkinson’s Disease (PD)               | 15–30 mg/kg| --                        | Bax, Bcl-2, Caspase-3, PDK1         | PI3K/AKT                              | RVT via activating the PI3K/AKT pathway could protect dopaminergic neurons from 6-hydroxy dopamine (6-OHDA)-induced apoptosis | [27]  |
| Spinal Cord Injury (SCI)               | 100 mg/kg, 40 μM | Primary microglia, neurons | Beclin-1, Caspase-3, LC3B          | PI3K                                  | RVT-primed exosomes via the PI3K pathway could promote the recovery of motor function in SCI rats | [28]  |
| **In vitro studies**                   |            |                            |                                     |                                       |                                                                          |       |
| Intervertebral Disc Degeneration (IVDD)| 200 mM     | NPCs                      | Caspase-3, NF-κB, GSK-3β             | PI3K/AKT/mTOR                         | RVT and 17β-estradiol via the PI3K/AKT/GSK-3β and PI3K/AKT/mTOR pathways could prevent IL-1β induced apoptosis in the human nucleus pulposus | [29]  |
| Intervertebral Disc Degeneration (MDD)| 10–200 μM  | NPCs                      | Caspase-3, MMP-3, MMP-13, COL2a-1, Aggrecan | PI3K/AKT                             | RVT and 17β-estradiol via the PI3K/AKT/caspase-3 pathway could play a role in apoptosis induced by interleukin-1β in rat nucleus pulposus cells | [30]  |
| Type of disease | Dose range | Cell line | Target                      | Pathway  | Function                                                                 | Refs. |
|----------------|------------|-----------|-----------------------------|----------|--------------------------------------------------------------------------|-------|
| IVDD           | 50–100 μM  | NP        | GAPDH, SOX9, Aggrecan, Collagen II | PI3K/AKT | RVT via activating the PI3K/AKT pathway could increase nucleus pulposus matrix synthesis | [31]  |
| IVDD           | 50 μM      | NP        | Aggrecan, Collagen II, Bedin-1, LC3 | PI3K/AKT | RVT via the PI3K/AKT pathway by activating autophagy could enhance matrix biosynthesis of nucleus pulposus cells | [32]  |
attenuation of the high glucose-induced oxidative stress, and reduction of apoptosis [39]. Resveratrol-induced suppression of PKC expression has also been shown to counteract NOX-associated endothelial to mesenchymal transition in endothelial cells of retina following exposure to high glucose [40]. Table 3 describes the impact of resveratrol on the expression of genes in the context of diabetic complications.

Gastrointestinal disorders
Resveratrol has been shown to exert protective effects against radiation-induced intestinal damage. This agent has amended the intestinal oxidative stress markers, malondialdehyde and glutathione levels, and enzymatic activity of catalase. Additionally, resveratrol has decreased the production of proinflammatory molecules TNF-α, NF-κB, and IL-1β in the intestine. These effects have been accompanied by down-regulation of PI3K, AKT, and mTOR in the intestinal tissue of irradiated animals. Therefore, resveratrol can be used as a potential adjuvant in radiotherapeutic regimens [43]. Moreover, resveratrol via the PI3K/AKT-mediated Nrf2 pathway could protect intestinal cells against oxidative stress [44]. The protective effects of resveratrol against liver fibrosis have been verified in different studies. Resveratrol can regulate the activity of hepatic stellate cells

### Table 3 Impact of resveratrol on the expression of genes in the context of diabetic complications

| Type of disease            | Dose range | Cell line     | Target          | Pathway                  | Function                                                                 | Refs. |
|----------------------------|------------|---------------|-----------------|--------------------------|--------------------------------------------------------------------------|-------|
| Diabetic cardiomyopathy (DCM) | 5–50 mg/kg, 10 μM | Ventricular myocytes | Bax, Bcl-2, Histone H3 | PI3K/AKT/FoxO3a           | RVT via the PI3K/AKT/FoxO3a pathway by inhibiting apoptosis could ameliorate cardiac dysfunction in DCM | [36]  |
| Type 1 diabetes (T1D)     | 40 mg/kg   | –             | GSK-3β, PTEN, Nrf2, NQO-1, HO-1, p62, Caspase-3, LC3II, Keap1 | AKT                      | RVT by AKT-mediated Nrf2 activation via p62-dependent Keap1 degradation could reduce testicular apoptosis in T1D mice | [41]  |
| Type 2 diabetes            | 100 mg/kg, 0–100 μM | HepG2         | miR-363-3p, FOXO1, G6PC | PI3K/AKT                 | RVT by upregulating mmu-miR-363-3p via the PI3K/AKT pathway could reverse high-fat diet (HFD)-induced insulin resistance | [37]  |
| Neuropathic pain           | 40 mg/mL   | –             | SIRT1/PGC1α      | PI3K/AKT                 | RVT via PI3K/AKT and SIRT1/PGC1α pathways could inhibit paclitaxel-induced neuropathic pain | [42]  |
| Diabetic nephropathy (DN)  | 10 mg/kg, 25 μM | Rat Mesangial Cell (RMC) | PAI-1           | AKT/NF-κB p65            | RVT via inhibiting AKT/NF-κB pathway could prevent mesangial cell proliferation and diabetes-induced renal inflammation | [35]  |
| In vitro studies           |            |               |                 |                          |                                                                          |       |
| DN                        | 10 μM      | PC12          | Bim, FoxO3a     | PI3K/AKT                 | RVT via the PI3K/AKT/FoxO3a pathway could attenuate the HG-induced oxidative stress and apoptosis in PC12 cells | [39]  |
| Diabetes mellitus         | 100 μM     | NP            | Caspase-3, Bcl-2, Bax, p53 | PI3K/AKT                 | RVT via activating PI3K/AKT pathway could attenuate high glucose-induced NP cell senescence and apoptosis | [38]  |
via modulating NF-κB and PI3K/AKT pathways [45]. Moreover, resveratrol via the miR-20a-mediated activation of the PTEN/PI3K/AKT pathway can inhibit LF [46]. Table 4 describes the impact of resveratrol on the expression of genes in the context of gastrointestinal disorders.

### Table 4: Impact of resveratrol on the expression of genes in the context of gastrointestinal disorders

| Type of disease | Dose range                  | Cell line | Target                      | Pathway                  | Function                                                                                       | Refs. |
|-----------------|-----------------------------|-----------|-----------------------------|--------------------------|------------------------------------------------------------------------------------------------|-------|
| In vivo studies |                              |           |                             |                          |------------------------------------------------------------------------------------------------|-------|
| Intestinal Injury | 20 mg/kg                    | –         | TNF-α, NF-κB, IL-1β         | PI3K/AKT/mTOR            | RVT via modulating PI3K/AKT/mTOR pathway could reduce intestinal inflammation in irradiated rats | [43]  |
| Liver Fibrosis (LF) | 40–200 mg/kg, 10–50 mg/mL   | HSC-T6    | miR-20a, α-SMA, TIMP-1, TGF-β1, LC3-II, LC3-I, Beclin1, Atg7 | PTEN/PI3K/AKT            | RVT via the miR-20a-mediated activation of the PTEN/PI3K/AKT pathway can inhibit LF           | [46]  |
| LF              | 20–50 mg/kg, 0–125 μg/mL    | LX-2      | α-SMA, Collagen-I, IkB-α, P65 | AKT, NF-κB               | RVT via the AKT/NF-κB pathways could attenuate the progression of LF                          | [47]  |
| In vitro studies |                              |           |                             |                          |                                                                                                |-------|
| Intestinal Damage | 0–50 μM                     | IPEC-J2, 293 T | Claudin-1, Occludin, ZO-1, Keap1, NFE2L2, SOD-1, HO-1, CAT, GSK-1, Nr12 | PI3K/AKT                | RVT via the PI3K/AKT-mediated Nrf2 pathway could protect IPEC-J2 cells against oxidative stress | [44]  |
| Hepatic Fibrosis | 3.125, 6.25, 12.5 μM        | T-HSC/Cl-6 | Collagen-I, α-SMA, TLR4, M8, LXR-α, LXR-β | PI3K/AKT, NF-κB          | RVT via modulating NF-κB and the PI3K/AKT pathway could regulate activated hepatic stellate cells (HSCs) | [45]  |

### Other disorders

Resveratrol has also been shown to inhibit ox-LDL-stimulated expression of TLR4 in activated platelets. This effect has been similarly seen in LPS-activated and puromycin-pretreated platelets. Mechanistically, resveratrol attenuates ox-LDL-stimulated phosphorylation of NF-κB and STAT3. Moreover, the suppressive impact of resveratrol on TLR4 expression has been correlated with the inhibition of phosphorylation of AKT. Combined administration of resveratrol and a PI3K inhibitor synergistically inhibits AKT phosphorylation and TLR4 expression. Besides, resveratrol has increased the expression of sirtuin 1 and phosphorylation of AMPK, which was decreased by ox-LDL. Besides, resveratrol has been shown to reduce platelet aggregation and adhesion and CD40L expression in ox-LDL-exposed platelets. Therefore, resveratrol can inhibit the TLR4-associated inflammatory responses in ox-LDL-induced platelets and might be used as an option for the treatment of thrombosis and atherosclerotic conditions [48]. In addition, a certain formulation of resveratrol-loaded nanoparticles has been shown to inhibit LPS-induced accumulation of leukocytes in the bronchoalveolar fluid. This effect has been accompanied by improvement of respiratory function, prevention of accumulation of leukocytes and neutrophils, and reduction of IL-6, KC, MIP-1α, MIP-2, MCP-1, and RANTES levels in lung tissues. Additionally, the mentioned formulation could inhibit MDA levels and SOD activity and block ERK and PI3K/AKT pathways after LPS stimulation [49]. In addition, resveratrol through suppression of PI3K/Nrf2/HO-1 pathway could inhibit oxidative stress, inflammation, and cell apoptosis and alleviate acute lung injury in septic rats [50]. The protective effect of resveratrol against sepsis-induced changes in the myocardium has been shown to be exerted through suppression of NF-κB and induction of the PI3K/AKT/mTOR pathway [51]. Table 5 describes the impact of resveratrol on the expression of genes in the context of other disorders.

### Effects of resveratrol on gene expression in neoplastic conditions

#### Hematological malignancies

Resveratrol can combat multidrug resistance (MDR) in leukemia. This substance has been shown to enhance the anti-proliferative effect of bestatin in the K562/ADR leukemia cell line. Concurrent treatment of leukemic cells with bestatin and resveratrol has decreased IC50 values of bestatin and increased activity of caspase-3 and caspase-8, indicating the potential effect of resveratrol in the enhancement of bestatin-induced apoptosis. Resveratrol has enhanced intracellular levels of bestatin via suppressing P-gp function and decreasing the expression level of P-gp, therefore increasing the anti-proliferative effect of
## Table 5 Impact of resveratrol on the expression of genes in the context of other disorders

| Type of disease                  | Dose range          | Cell line                  | Target                          | Pathway                  | Function                                                                                     | Refs. |
|----------------------------------|---------------------|----------------------------|---------------------------------|--------------------------|-----------------------------------------------------------------------------------------------|-------|
| **In vivo studies**              |                     |                            |                                 |                          |                                                                                            |       |
| Acute Lung Injury (ALI)          | 2.5–10 mg/kg        | –                          | IL-6, KC, MIP-1α, MIP-2, MCP-1, RANTES | PI3K/AKT, ERK           | Delivering RVT by polymeric nanocapsules via the ERK/PI3K/AKT pathways could ameliorate LPS-induced ALI | [49]  |
| Sepsis                           | 30 mg/kg            | –                          | MIP-2, IL-1β, IL-10, Caspase-3   | PI3K/Nf2/HO-1            | RVT via inhibiting PI3K/Nf2/HO-1 pathway could inhibit oxidative stress, inflammation, and cell apoptosis to alleviate ALI in septic rats | [50]  |
| Sepsis                           | 60 mg/kg            | –                          | IL-6, IL-1β, TLR4, Caspase-3, Bax, Bcl2, NF-κB | PI3K/AKT/mTOR          | RVT via inhibiting the NF-κB and activating the PI3K/AKT/mTOR pathway could protect the myocardium in sepsis | [51]  |
| Allergic Diseases                | 10 mg/kg, 10–100 μM | BMMCs, F5MCs, PBMCs        | IL-6, IL-13, TNF-α, NF-κB, IKKα/β, p65, P-38, Syk, Gab2 | MK2/PI3K/AKT           | RVT via inhibiting the PI3K/AKT pathway could inhibit the development of obesity-related OA | [52]  |
| Osteoarthritis (OA)              | 45 mg/kg            | SW1353                     | TLR4, MyD88, TRIF, IL-1β, NF-κB p65 | PI3K/AKT                | RVT via inhibiting TLR4 via the activation of the PI3K/AKT pathway could inhibit the development of OA | [53]  |
| Chronic Unpredictable Mild Stress (CUMS) | 40–80 mg/kg | –                          | TNF-α, IL-6, IL-1β, Bax, Bcl-2   | AKT/GSK-3β              | RVT via activating the AKT/GSK-3β pathway could exert a protective effect in CUMS–induced depressive-like behavior | [54]  |
|                                 | –                   | 100 mg/kg, 20 μM           | klf5, c-Myc, Cav-1              | PI3K/PKD1/AKT           | RVT via inhibiting the PI3K/PKD1/AKT pathway could activate klf5 phosphorylation and then attenuate the interaction of klf5 with c-Myc | [55]  |
|                                 | –                   | 100 mg/kg 40–100 μM       | hPASMC                         | PI3K/AKT                | RVT via the PI3K/AKT pathway could prevent hypoxia-induced arginase II expression and proliferation of hPASMC | [56]  |
| **In vitro studies**             |                     |                            |                                 |                          |                                                                                            |       |
| Thrombosis and atherosclerosis   | 1–100 μM            | Platelet                   | PECAM-1, TLR4, STAT3, NF-κB p65, Sirt1 | AKT, AMPK               | RVT via STAT3 and AKT pathways could suppress TLR4 activation in oxidized low-density lipoprotein-activated platelets | [48]  |
|                                 | –                   | 15 μmol/L                  | BMSCs, P3                      | SIRT1/AKT/FOXO1        | RVT via activating the SIRT1/AKT/FOXO1 pathway could reverse myogenic induction suppression caused by high glucose | [57]  |
|                                 | –                   | 20 μM                      | Chondrocytes                   | Collagen-II, COX-2, PGE2, JNK, P38 | AKT, ERK, MAPK                                                              | [58]  |
bestatin in K562/ADR cells. Mechanistically, resveratrol has been shown to decrease AKT and mTOR phosphorylation without affecting the phosphorylation of JNK or ERK1/2 [59]. Moreover, resveratrol can regulate apoptosis and proliferation of leukemia cells through modulation of PTEN/PI3K/AKT [60]. Table 6 describes the impact of resveratrol on the expression of genes in the context of hematological malignancies.

Gastrointestinal cancers
Resveratrol has protective effects against bile acid-induced gastric intestinal metaplasia. Resveratrol has been shown to decrease the expression of CDX2 and enhance the activity of FoxO4 in gastric cell lines. Based on the bioinformatics and chromatin-immunoprecipitation analyses, FoxO4 has been shown to bind with the promoter region of CDX2. These effects are mediated through the enhancement of nuclear translocation phospho-FoxO4. In addition, resveratrol enhances FoxO4 phosphorylation via modulation of the PI3K/AKT pathway. Taken together, resveratrol can decrease bile acid-induced gastric intestinal metaplasia via the PI3K/AKT/p-FoxO4 cascade. Thus, it has a protective effect against bile acid-induced gastric intestinal metaplasia particularly those associated with bile acid reflux [63]. In addition, through regulating the PTEN/PI3K/AKT pathway, resveratrol could induce cell cycle arrest in human gastric cancer cells [64]. Besides, via MARCH-1-induced regulation of the PTEN/AKT pathway, resveratrol can inhibit the malignant progression of hepatocellular carcinoma [65]. Resveratrol can also up-regulate connexin43 and inhibit the AKT pathway, therefore sensitizing colorectal cancer cells to cetuximab [66]. Table 7 describes the impact of resveratrol on the expression of genes in the context of gastrointestinal cancers.

Reproductive system cancers
Resveratrol has been shown to decrease expression levels of MTA1, a constituent of the nucleosome remodeling and deacetylating (NuRD) complex which is up-regulated in numerous malignancies [75]. Moreover, resveratrol can enhance acetylation and reactivation of PTEN through suppression of the MTA1/HDAC complex, leading to blockage of the AKT pathway. Further experiments in the orthotopic model of prostate cancer have verified the effects of resveratrol in the enhancement of PTEN expression, reduction of p-AKT levels, in suppression of proliferation. Therefore, resveratrol can decrease the activity of survival pathways of prostate cancer via modulation of the MTA1/HDAC axis [76]. In ovarian cancer cells, resveratrol can induce apoptosis and impair glucose uptake via AKT/GLUT1 axis [77]. Moreover, resveratrol has been shown to induce cell death via ROS-dependent inactivation of Notch1/PTEN/AKT cascade [78]. Table 8 describes the impact of resveratrol on the expression of genes in the context of reproductive system cancers.

Lung cancer
Resveratrol has been shown to inhibit the expression of XRCC1 and increase the etoposide-associated apoptosis in non-small cell lung cancer (NSCLC) cells. Thus, the inhibitory role of resveratrol on the expression of XRCC1 improves the sensitivity of these cells
Table 7  Impact of resveratrol on the expression of genes in the context of gastrointestinal cancers

| Type of cancer | Dose range | Cell line | Target | Pathway | Function | Refs. |
|----------------|------------|-----------|--------|---------|----------|-------|
| *In vivo studies* | | | | | | |
| Gastric cancer (GC) | 50 mg/kg, 10–200 mg/L | SGC7901, SGC7901/DOX, MGC803 | TSC1, TSC2, p70S6K, Caspase-3/9, Vimentin, E-cadherin | PTEN/AKT, mTOR | RVT via modulating PTEN/AKT pathway by inhibiting EMT could reverse doxorubicin resistance in GC | [67] |
| Hepatocellular Carcinoma (HCC) | 0–100 mg/kg, 20–80 μM | HepG2, Hep3B | MARCH-1, STAT3, VEGF, Bcl-2 | PTEN/AKT | RVT via MARCH-1 induced regulation of the PTEN/AKT pathway and inhibit malignant progression of HCC | [65] |
| Colorectal Cancer (CRC) | 1 mg/kg 5 μg/mL | HCT116, CT26 | Cx43, EGFR, NF-κB p65, IκKα, IκBa, AKT, PI3K, mTOR, MAPK | PTEN/PI3K/AKT, Wnt/β-catenin | RVT via upregulating connexin43 and inhibition of the AKT pathway could sensitize CRC cells to cetuximab | [66] |
| CRC | 50–150 mg/kg, 0–80 μM | HCT116, SW480 | PCNA, Caspase-3, GSK-3β, PTEN/PI3K/AKT, Wnt/β-catenin | PTEN/PI3K/AKT, Wnt/β-catenin | RVT via the Wnt/β-catenin and PTEN/P3K/AKT pathways could play a role in human colon cancer cell proliferation | [68] |
| CRC | 150 mg/kg, 0–240 μmol/L | SW480 and SW620 | N-cadherin, E-cadherin, Vimentin | AKT/GSK-3β/Snail | RVT via the AKT/GSK-3β/Snail pathway could inhibit the metastasis and invasion of CRC cells | [69] |
| *In vitro studies* | | | | | | |
| Gastric intestinal metaplasia (GIM) | 200 μM | GES-1, AGS, BGC823, SGC7901, MKN45, MKN28, AZ521, HCT116 | CDX2, Villin1, Klf4, Cadherin17, Muc2 | PTEN/PI3K/p-FoxO4 | RVT via the PI3K/AKT/p-FoxO4 pathway could inhibit bile acid-induced GIM | [63] |
| GC | 50–200 μmol/L | MGC803 | GSK3β, Cyclin-D1 | PTEN/PI3K/AKT | RVT via regulating the PTEN/PI3K/AKT pathway could induce cell cycle arrest in human gastric cancer MGC803 cells | [64] |
| HCC | 0–200 μM | HepG2 | FoxO3a/Bim | AKT | RVT via modulating AKT/FoxO3a/Bim pathway could induce apoptosis in HepG2 cells | [70] |
| HCC | 100 μM | HepG2, Bel-7402, SMMC-7721 | SIRT1, Bcl-2, Caspase-3/7, PARP, PCNA, Bax | PTEN/PI3K/AKT | RVT via SIRT1 mediated post-translational modification of PI3K/AKT signaling could inhibit migration and proliferation in HCC cells | [71] |
| CRC | 10–40 μM | DLD1, HCT15 | Cyclin-D1, Cyclin-E2, Bcl-2, p53, Bax | AKT/STAT3 | RVT via targeting the AKT/STAT3 pathway could suppress colon cancer growth | [72] |
Concentration of resveratrol and its metabolites has been assessed in the colorectal tissues of humans who received resveratrol in a clinical study on colorectal cancer patients who took eight daily doses of resveratrol at 0.5 or 1.0 g prior to surgical resection of tumors. This study has confirmed tolerability of resveratrol. More importantly, these doses of resveratrol have been shown to produce sufficient concentrations for induction of anti-cancer effect in the gastrointestinal tract [74].

| Type of cancer | Dose range | Cell line | Target | Pathway | Function | Refs. |
|----------------|------------|-----------|--------|---------|----------|-------|
| CRC            | 40–60 μM   | HCT116, 293 T | BMP7, GFP, PTEN, BAD, Bcl-2, Smad1/5/8 | PI3K/AKT | RVT via upregulating BMP7 could inactivate PI3K/AKT signaling in human colon cancer cells | [73] |
Moreover, through suppressing the PI3K/AKT-HK2 pathway, resveratrol can play a role in the clinical prevention and treatment of NSCLC [47]. Resveratrol also activates SIRT1 and stimulates protective autophagy in NSCLC cells through suppression of AKT/mTOR and induction of p38-MAPK [83]. Finally, resveratrol can sensitize lung cancer cells to TRAIL via suppressing the AKT/NF-κB pathway [84]. Table 9 describes the impact of resveratrol on the expression of genes in the context of lung cancer.

Other cancers

Resveratrol has been shown to suppress the proliferation of both parental and vemurafenib-resistant melanoma cell lines. Moreover, it can reduce AKT phosphorylation in these cells. Therefore, it can reverse vemurafenib resistance in patients receiving BRAF inhibitors [86]. Moreover, by inhibiting the PI3K/AKT/mTOR pathway, it could promote autophagy and suppress the growth of melanoma cells [87]. Resveratrol can also sensitize lung cancer cells to TRAIL via suppressing the AKT/NF-κB pathway [84]. Table 9 describes the impact of resveratrol on the expression of genes in the context of lung cancer.

Table 8 Impact of resveratrol on the expression of genes in the context of cancers of the reproductive system

| Type of cancer | Dose range | Cell line | Target | Pathway | Function | Refs. |
|---------------|------------|-----------|--------|---------|----------|-------|
| **In vivo studies** | | | | | | |
| Prostate Cancer (PCa) | 50 mg/kg 5–100 μM, DU145, PC3M, 293 T | MTA1, HDAC, ERK1/2, HDAC1, HDAC2, Lamin-A, myc, Flag | PTEN, AKT | RVT by regulating the PTEN/AKT pathway via inhibiting the MTA1/HDA unit could affect the progression and survival pathways of prostate cancer | [76] |
| **In vitro studies** | | | | | | |
| PCa | 25–200 μM | LNCaP, RWPE-1, LNCaP-B | ARV7, Bax, Bcl-2, AR | PI3K/AKT | RVT via PI3K/AKT pathway and ARV7 could promote apoptosis in LNCaP prostate cancer cells | [79] |
| PCa | 0–50 μM | PC-3 | E-cadherin, Vimentin, Bax, Bcl-2, Caspase-3/9 | PI3K/AKT | RVT via downregulating the PI3K/AKT pathway could suppress the EMT in PC-3 cells | [80] |
| Ovarian Cancer | 50 mM | PA-1, OVCA13, MDAH2774, SKOV3, PBMC, RBC, OSE1, OSE2 | P70s6K, mTOR, 4EBP1, GLUT2, GLUT3, GLUT4, GLUT1 | AKT | RVT via AKT/GLUT1 axis could induce apoptosis in ovarian cancer cells by impairing glucose uptake | [77] |
| Ovarian Cancer | 0–200 μM | A2780, SKOV3 | Caspase-3 | Notch1/PTEN/AKT | RVT via notch1/PTEN/AKT signaling could induce cell death in ovarian cancer cells | [78] |

Discussion

Several clinical trials have assessed the efficacy, safety, and pharmacokinetics of resveratrol [101]. It has potential beneficial effects in diverse pathological conditions such as diabetes mellitus, obesity, hypertension, neoplastic conditions, Alzheimer’s disease, and cardiovascular disorders [101]. However, the therapeutic efficacy of resveratrol seems to be dependent on several factors [102]. For instance, the efficacy of resveratrol has been higher in certain types of cancer compared with others. Moreover, additional clinical trials should be conducted to assess the effects of resveratrol in the treatment of Alzheimer’s disease and stroke. Studies in the context of cardiovascular disorders have shown beneficial effects of resveratrol.
However, these effects depend on demographics features, since it has not been effective in extremely overweight persons, even has been harmful in schizophrenic patients [103].

Another important note is that the optimal dosage of resveratrol which can induce the maximum beneficial effects without raising toxic effects remains to be identified. A number of studies have reported toxic and adverse effects after consumption of resveratrol [104]. Thus, widespread investigations on the long-term effects of resveratrol in human subjects are needed. Moreover, the interactions between resveratrol and other therapeutic agents should be assessed [104]. A possible adverse effect of resveratrol might be mediated by down-regulation of Akt which induces ROS generation and endothelial cell injury in a dose-dependent manner [105]. Moreover, resveratrol has been shown to alter redox state of human endothelial cells and cause cellular death through a mitochondrial-dependent route [106].

Notably, resveratrol has been found to affect the expression of several genes including cytokine coding genes, caspases, matrix metalloproteinases, adhesion molecules, and growth factors [101]. In addition to the mentioned protein coding genes, evidence from in vitro and in vivo assays has shown the direct effects of resveratrol on several non-coding genes and possible implication of these transcripts in the therapeutic effects of resveratrol [107]. Moreover, it can modulate the activity of several signaling pathways such as PI3K/AKT, Wnt, NF-κB, and Notch pathways [101]. Among the mentioned pathways, the regulatory effects of resveratrol on the activity of the PI3K/AKT pathway have been better appraised in different contexts. In the context of neoplastic conditions, resveratrol not only inhibits malignant behavior of cells and epithelial-mesenchymal transition but also sensitizes neoplastic cells to anti-cancer drugs such as rapamycin [89], doxorubicin [67], vemurafenib [86], cetuximab [66], etoposide [82] and docetaxel [88]. Therefore, it can be used as an adjuvant to enhance the efficacy of several types of anti-cancer modalities ranging from conventional chemotherapeutic agents to targeted therapies. The effects of resveratrol in the suppression of growth of cancer stem cells have been validated in some types of cancers particularly glioblastoma [91]. This property of resveratrol should be appraised in other cancers to find whether it can be used as a drug to combat tumor metastasis and recurrence.

**Table 9** Impact of resveratrol on the expression of genes in the context of lung cancer

| Type of cancer | Dose range | Cell line | Target | Pathway | Function | Refs. |
|---------------|------------|-----------|--------|---------|---------|-------|
| **In vivo studies** | | | | | | |
| Non-Small Cell Lung Cancer (NSCLC) | 30 mg/kg 0–100 μM | H460, H1650, HCC827 | HK2, Caspase-3, PARP, AKT, ERK1/2, EGFR | RVT via suppressing the PI3K/AKT-HK2 pathway could play a role in the clinical prevention and treatment of NSCLC | [47] |
| **In vitro studies** | | | | | | |
| NSCLC | 25–200 μM | H1703, H1975 | XRCC1 | AKT, ERK1/2 | RVT via downregulating ERK1/2 and AKT-mediated XRCC1 could enhance the chemosensitivity to etoposide in NSCLC cells | [82] |
| NSCLC | 200 μM | AS49, H1299 | Beclin-1, LC3 II/I, SIRT1, P62, p70S6K | AKT/mTOR, p38-MAPK | RVT by activating p38-MAPK and inhibiting the AKT/mTOR pathway could induce protective autophagy in NSCLC cells | [83] |
| NSCLC | 0–50 μM | AS49, HCC-15 | LC3-II, P62, p53, Bax, Bcl-2, Bcl-xl, Caspase-3/8, PUMA, Cytochrome-c | AKT, NF-κB | RVT via suppressing the AKT/NF-κB pathway could sensitize lung cancer cells to TRAIL | [84] |
| Small Cell Lung Cancer (SCLC) | 40 μg/mL | H446 | c-Myc, AIF, Bcl-2, Bax, Bcl-xl, Cytochrome-c | PI3K/AKT | RVT via the PI3K/AKT/c-Myc pathway could inhibit viability in SCLC H446 cells | [85] |
Table 10  Impact of resveratrol on the expression of genes in the context of other cancers

| Type of cancer                     | Dose range     | Cell line            | Target                  | Pathway                        | Function                                                                 | Refs. |
|-----------------------------------|----------------|----------------------|-------------------------|--------------------------------|--------------------------------------------------------------------------|-------|
| Breast cancer (BCa)               | 50 mg/kg, 10–200 mg/L | MCF-7/DOX, MCF-7, MDA-MB-231 | Caspase-3, P70S6K       | PI3K/AKT/mTOR                  | RVT via inhibiting PI3K/AKT/mTOR pathway could play a role in DOX resistance in breast neoplasm | [90]  |
| Papillary Thyroid cancer (PTC)    | 30 mg/kg 50 μM | KTC-1,TPC-1          | Caspase-3/8/9, Bax, Bcl-xl, Mcl-1, p70S6K | PI3K/AKT/mTOR                 | RVT via the PI3K/AKT/mTOR pathway could promote the anti-tumor effects of rapamycin in papillary thyroid cancer | [89]  |
| Glioblastoma multiforme (GBM)     | 10 mg/kg, 0–20 μM | GICs                 | IKKα/β, JNK, mTOR, ERK1/2, IkBa, p38, MMP-2, Lamin-A, Nestin, GFAP | PI3K/AKT/NF-κB                | RVT via downregulating PI3K/AKT/NF-κB pathway could inhibit invasion of glioblastoma-initiating cells (GICs) | [91]  |
| In vitro studies                  |                |                      |                         |                                |                                                                          |       |
| Melanoma                          | 4 μM-18 μM     | Human melanoma cell  | –                       | AKT                            | RVT via dephosphorylation of AKT could overcome resistance to vemurafenib in BRAF-mutated melanoma cells | [86]  |
| Melanoma                          | 100 μM         | B16                  | LC3-I, LC3-II, Beclin-1, S6K, 4E-BP1 | Ceramide/AKT/mTOR              | RVT via the ceramide/AKT/mTOR pathway could trigger protective autophagy in melanoma B16 cells | [87]  |
| Melanoma                          | 0–100 μM       | B16-F10, A375        | Beclin-1, Caspase-9, P62, LC3II | PI3K/AKT/mTOR                  | RVT via inhibiting the PI3K/AKT/mTOR pathway could promote autophagy and suppress melanoma growth | [92]  |
| Pheochromocytoma                  | 10–1000 μM     | PC12                 | Caspase-3, iNOS         | PI3K, AKT/p38 MAPK             | RVT via AKT/p38 MAPK signaling could attenuate apoptosis, and protect neuronal cells from isoflurane-induced inflammation | [93]  |
| BCa                               | 10–25 μM       | SK-BR-3, MCF7,T47D, MDA-MB-231 | Caspase-7/8, JNK, P38, XIAP, Survivin, Bcl-2 | AKT, HER-2, MAPK              | RVT via inhibiting docetaxel-mediated activation of the HER-2/AKT axis could sensitize BCa cells to docetaxel-induced cytotoxicity | [88]  |
| Bladder cancer                    | 0–50 μmol/L    | T24, 5637, SV-HUC-1  | miR-21, Bcl-2, Caspase-3 | AKT                            | RVT via miR-21 regulation of the AKT/Bcl-2 pathway could induce apoptosis of bladder cancer cells | [94]  |
| Chondrosarcoma                    | 25–100 μM      | JJ01 2, SW1353       | MMP2, MMP9              | PI3K/AKT/MAPK                  | RVT via regulating the PI3K/AKT/MAPK pathway could inhibit cell proliferation and induce cell apoptosis in chondrosarcoma cells | [95]  |
| Renal cell carcinoma (RCC)        | 0–100 μM       | ACHN, A498, HK-2     | N-cadherin, Vimentin, Snail, MMP-2/9, E-cadherin, TIMP-1 | AKT, ERK1/2                   | RVT via inactivating the AKT and ERK1/2 pathways could inhibit proliferation and migration in RCC cells | [96]  |
| Type of cancer   | Dose range | Cell line          | Target                                                                 | Pathway                  | Function                                                                 | Refs. |
|-----------------|------------|--------------------|------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------|-------|
| Oral cancer     | 50 μM      | CAR, CAL 27        | LC3-II/I, Caspase-3/9, Atg-5/7/1/2/1/4, Beclin-1, Atg16L1, Apaf-1, AIF, Bcl-2, Bax, Bad | AKT/mTOR, AMPK           | RVT via the AMPK and AKT/mTOR pathway could regulate autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells | [97]  |
| Neuroblastoma (NB) | 10–100 μM | SK-N-SH, SH-SY5Y, SK-N-Be2, SMS-KCNR, NB1691 | GSK3β, IRS-1, Survivin, PP1α, α-tubulin | AKT                      | RVT via inactivating AKT by increasing PP1α activity could potentiate 2-DG-induced ER stress and NB cell death | [98]  |
An important issue in the clinical application of resveratrol is the identification of the best route and formulations of this agent. A certain nanoformulation of resveratrol has been proved to be an effective approach for improving the protective effects of resveratrol against lung injury, proposing that the modified-release preparation of this substance can be effective in this situation [49]. Further studies are needed to appraise the efficacy of this formulation in other conditions.

Conclusion
Taken together, resveratrol has several therapeutic effects including modulation of immune responses and ROS formation, suppression of malignant behavior of cancer cells, and sensitization of these cells to anti-cancer drugs. Increasing the bioavailability of this agent and identification of the most appropriate route of administration of this agent are important changes that should be addressed before the extensive application of resveratrol in clinical settings.

Acknowledgements
Not applicable.

Author contributions
SGF wrote the manuscript and revised it. MT, SAA designed and supervised the study. HS, ZB, BMS, SFT, SGB and BMH collected the data and designed the tables and figures. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participant
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare they have no competing interests.

Author details
1Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 2Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. 3Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran. 4Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq. 5Center of Research and Strategic Studies, Lebanese French University, Erbil, Kurdistan Region, Iraq. 6Department of Pharmacology, College of Pharmacy, Birjand University of Medical Sciences, Birjand, Iran. 7Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan. 8Institute of Human Genetics, Jena University Hospital, Jena, Germany. 9Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 10Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: 7 December 2021 Accepted: 21 September 2022
Published online: 30 September 2022

References
1. Frémont L. Biological effects of resveratrol. Life Sci. 2000;66(8):663–73 (Epub 2000/02/19. eng).
2. Shrikanta A, Kumar A, Govindaswamy V. Resveratrol content and antioxidant properties of underutilized fruits. J Food Sci Technol. 2015;52(1):383–90 (Epub 05/04. eng).
3. Baell J, Walters MA. Chemistry: chemical con artists foil drug discovery. Nature. 2014;513(7519):481–3 (Epub 2014/09/26. eng).
4. Ingólfsson HI, Thakur P, Herold KF, Hobart EA, Ramsey NB, Periolo X, et al. Phytochemicals perturb membranes and promiscuously alter protein function. ACS Chemical Biol. 2014;9(8):1788–98 (Epub 2014/06/06. eng).
5. Valletta A, Ioza LM, Leonelli F. Impact of environmental factors on stillbene biosynthesis. Plants. 2021;10(1):90.

6. Madhav NV, Shakyi AK, Shakya P, Singh K. Orthonmocosal drug delivery systems: a review. J Control Release. 2009;140(1):2–11. (Epub 2009/08/12. eng).

7. Walle T, Heiße F, DeLegge MH, Oats JE Jr, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos. 2004;32(12):1377–82. (Epub 2004/08/31. eng).

8. Luca SV, Macovei I, Bujor A, Miron A, Skalicka-Woźniak K, Aprotosoaie A, et al. Bioactivity of dietary polyphenols: the role of metabolites. Crit Rev Food Sci Nutr. 2020;60(6):626–59. (Epub 2019/01/08. eng).

9. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006;5(6):493–506. (Epub 2006/05/30. eng).

10. Poulsen MM, Fjeldborg K, Onstrup MJ, Kjær TN, Nahr MK, Pedersen SB. Resveratrol and inflammation: challenges in translating pre-clinical findings to improved patient outcomes. Biochim Biophys Acta. 2015;1852(6):1124–36.

11. Bastianetto S, Ménard C, Quirion R. Neuroprotective action of resveratrol. Biochim Biophys Acta. 2015;1852(6):1195–201.

12. Khan MA, Chen H-C, Wan X-X, Tania M, Xu A-H, Chen F-Z, et al. Regulatory effects of resveratrol on antioxidant enzymes: a mechanism of growth inhibition and apoptosis induction in cancer cells. Mol Cells. 2013;35(3):219–25.

13. Guan P, Sun Z-M, Wang N, Zhou J, Luo Y-S, et al. Resveratrol prevents chronic intermittent hypoxia-induced cardiac hypertrophy by targeting the PI3K/AKT/mTOR pathway. Life Sci. 2019;233: 116748.

14. Hou Y, Wang K, Wan W, Cheng Y, Pu X, Ye X, et al. Resveratrol enhanced FOXO3 phosphorylation via synergetic activation of SIRT1 and PI3K/Akt signaling to improve the effects of exercise in elderly rat hearts. Age. 2014;36(5):1–10.

15. Chong E, Chang S-L, Hisao Y-W, Singhal R, Liu S-H, Leh a T, et al. Resveratrol, a red wine antioxidant, reduces atrial fibrillation susceptibility in the failing heart by PI3K/AKT/eNOS signaling pathway activation. Heart Rhythm. 2015;12(5):1046–56.

16. Zhang X, Huang L, Hua L, Feng H, Shen B. Resveratrol protects myocardial apoptosis induced by ischemia-reperfusion in rats with acute myocardial infarction via blocking PI3K/Akt/e-NOS pathway. Eur Rev Med Pharmacol Sci. 2019;23(4):1789–96.

17. Lin C-H, Lin C-C, Ting W-I, Pai P-Y, Kuo C-H, Ho T-J, et al. Resveratrol enhanced FOXO3 phosphorylation via synergetic activation of SIRT1 and PI3K/Akt signaling to improve the effects of exercise in elderly rat hearts. Age. 2014;36(5):1–10.

18. Guo D, Xie J, Zhao J, Huang T, Guo X, Song J. Resveratrol protects early brain injury after subarachnoid hemorrhage by activating autophagy and inhibiting apoptosis mediated by the Akt/mTOR pathway. Neurol Rep. 2018;29(5):368.

19. Hou Y, Wang K, Wan W, Cheng Y, Pu X, Ye X. Resveratrol provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR pathway after stroke in rats. Genes Diseases. 2018;5(3):245–55.

20. Lei J, Chen Q. Resveratrol attenuates brain damage in permanent focal cerebral ischemia via activation of PI3K/Akt signaling pathway in rats. Neurol Rep. 2018;40(12):1014–20.

21. Hui Y, Chengyong T, Cheng L, Haixia H, Yuanda Z, Weihua Y. Resveratrol attenuates the cytotoxicity induced by amyloid-β 1–42 in PC12 cells by upregulating heme oxygenase-1 via the PI3K/Akt/Nrf2 pathway. Neuronal Res. 2018;43(2):297–305.

22. Shati AA, Alfaifi MY. Trans-resveratrol inhibits tau phosphorylation in PC12 cells exposed to high glucose. Antioxidants. 2021;10(2):224.

23. Sheng Z, Li Q, Meng Z, Li X, Wang L. Trans-resveratrol protects the brains of control and cadmium chloride ‑treated rats by activating autophagy via activation of PI3K/Akt/GSK ‑3 β pathway. Arch Physiol Biochem. 2020;171319.

24. Gao J, Zhang Q, Song L. Resveratrol enhances matrix biosynthesis of nucleus pulposus cells through activating autophagy via the PI3K/ Akt pathway under oxidative damage. 2018. Biosci Rep. https://doi.org/10.1042/BSR20180544.

25. Turner RS, Thomas RG, Craft S, van Dyck CH, Mintzer J, Reynolds BA, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85(16):1383–91.

26. Wang H, Yuan C, Li J, Tan T-P, Wu S-J, Fu H-Y, et al. Resveratrol protects against brain ischemia reperfusion injury in mice with enhanced FOXO3 phosphorylation via synergetic activation of SIRT1 and PI3K/Akt signaling pathway under mechanical compression in a disc organ culture. 2017. Biosci Rep. https://doi.org/10.1042/BSR20171454.

27. Liu M-H, Yuan C, He J, Tan T-P, Wu S-J, Fu H-Y, et al. Resveratrol protects PC12 cells from high glucose-induced neurotoxicity via PI3K/Akt/ FoxO3a pathway in a rat model of diabetic cardiomyopathy. J Cardiovasc Pharmacol. 2017;70(3):184–93.

28. Fan Y, Li Y, Huang S, Xu H, Li H, Liu B. Resveratrol‑primed exosomes strongly promote the recovery of motor function in SCI rats by activating autophagy and inhibiting apoptosis via the PI3K signaling pathway. Neurosci Lett. 2020;736: 135262.

29. Bai X, Guo X, Zhang F, Zheng L, Ding W, Yang S. Resveratrol combined with 17 β‑estradiol prevents L‑1‑β induced apoptosis in human nucleus pulposus via the PI3K/AKT/Mtor and PI3K/AKT/GSK‑3 β pathway. J Invest Surg. 2020. https://doi.org/10.1080/09841939.2019. 1705941.

30. Yang S-D, Ma L, Yang D-L, Ding W-Y. Combined effect of 17 β‑estradiol and resveratrol against apoptosis induced by interleukin‑1β in rat nucleus pulposus cells via PI3K/Akt/caspase‑3 pathway. PeerJ. 2016;4: e1640.

31. Han X, Leng X, Zhao M, Wu M, Chen A, Hong G, et al. Resveratrol increases nucleus pulposus matrix synthesis through activating the PI3K/Akt signaling pathway under mechanical compression in a disc organ culture. 2017. Biosci Rep. https://doi.org/10.1042/BSR20 171319.

32. Zhuang Y, Wu H, Wang X, He J, He S, Yin Y. Resveratrol attenuates oxidative stress‑induced intestinal barrier injury through activating the ROS-mediated PI3K/Akt pathway. 2018. Biosci Rep. https://doi.org/10.1042/BSR20171454.

33. Liu M-H, Yuan C, He J, Tan T-P, Wu S-J, Fu H-Y, et al. Resveratrol protects PC12 cells from high glucose-induced neurotoxicity via PI3K/Akt/ FoxO3a pathway. Cell Mol Neurobiol. 2015;35(4):513–22.

34. Giordo R, Nasrallah GK, Posadino AM, Galimi F, Capobianco G, Eid AH, et al. Resveratrol‑elicited plc inhibition counteracts nor‑medicated endothelial to mesenchymal transition in human retinal endothelial cells exposed to high glucose. Antioxidants. 2021;10(2):224.

35. Zhao Y, Song W, Wang Z, Wang Z, Jin X, Xu J, et al. Resveratrol attenuates testicular apoptosis in type 1 diabetic mice: Role of Akt-mediated Nrf2 activation and p62-dependent Keap1 degradation. Redox Biol. 2018;14:609–17.

36. Li X, Yang S, Wang L, Liu P, Zhao S, Li H, et al. Resveratrol inhibits paclitaxel-induced neuropathic pain by the activation of PI3K/Akt and SIRT1/PGC1α pathway. J Pain Res. 2019;12:879.

37. Radwan RR, Karam HM. Resveratrol attenuates intestinal injury in irradiated rats via PI3K/Akt/mTOR signaling pathway. Environ Toxicol. 2020;35(2):223–30.

38. Zhuang Y, Wu H, Wang X, He J, He S, Yin Y. Resveratrol attenuates oxidative stress‑induced intestinal barrier injury through PI3K/Akt-mediated...
et al. Cancer Cell International          (2022) 22:298

45. Zhang DQ, Sun P, Jin Q, Li X, Zhang Y, Zhang YJ, et al. Resveratrol regu‑

46. Zhu L, Mou Q, Wang Y, Zhu Z, Cheng M. Resveratrol contributes to the

47. Zhang H, Sun Q, Xu T, Hong L, Fu R, Wu J, et al. Resveratrol attenuates

48. Sun J, Zhang M, Chen K, Chen B, Zhao Y, Gong H, et al. Suppression

49. de Oliveira MTP, de Sá CD, de Souza ÉT, Guterres SS, Pohlmann AR, Silva

50. Wang Y, Wang X, Zhang L, Zhang R. Alleviation of acute lung injury in

52. Nakajima S, Ishimaru K, Kobayashi A, Yu G, Nakamura Y, Oh‑Oka K, et al.

54. Shen J, Qu C, Xu L, Sun H, Zhang J. Resveratrol exerts a protective effect

55. Yang H, Chen Q, Sun F, Zhao N, Wen L, Li L, et al. Down‑regulation of the

58. Eo SH, Cho HS, Kim SJ. Resveratrol regulates type II collagen and COX‑2

61. Guan H, You Z, Wang C, Fang F, Peng R, Mao L, et al. MicroRNA‑200a

64. Jing X, Cheng W, Wang S, Li P, He L. Resveratrol induces cell cycle arrest

65. Dai H, Li M, Yang W, Sun X, Wang P, Wang X, et al. Resveratrol inhibits

66. Wang Y, Wang W, Wu X, Li C, Huang Y, Zhou H, et al. Resveratrol sensitizes
colorectal cancer cells to cetuximab by connexin 43 upregulation‑induced Akt inhibition. Front Oncol. 2020:10.383.

67. Xu J, Liu D, Niu H, Zhu G, Xu Y, Ye D, et al. Resveratrol reverses Doxo‑rubcin resistance by inhibiting epithelial‑mesenchymal transition (EMT) through modulating PTEN/AKT signaling pathway in gastric cancer. J Exp Clin Cancer Res. 2017;36(1):1–14.

68. Liu Y‑Z, Wu K, Huang J, Liu Y, Wang X, Meng Z‑J, et al. The PTEN/PI3K/ Akt and Wnt/β‑catenin signaling pathways are involved in the inhibitory effect of resveratrol on human colon cancer cell proliferation. Int J Oncol. 2014:45(1):104–12.

69. Yuan L, Zhou M, Huang D, Wasan HS, Zhang K, Sun L, et al. Resveratrol inhibits the invasion and metastasis of colon cancer through reversal of epithelial‑mesenchymal transition via the AKT/GSK3β/ Snail signaling pathway. Mol Med Rep. 2019:20(3):2783–95.

70. Liu MH, Lin XL, Li J, He J, Tan TP, Wu SJ, et al. Resveratrol induces apoptosis through modulation of the AKT/FoxO3a/Bim pathway in HepG2 cells. Mol Med Rep. 2016;13(2):1689–94.

71. Chai R, Fu H, Zheng Z, Liu T, Li S, Li G. Resveratrol inhibits proliferation and migration through SIRT1‑mediated post‑translational modification of PI3K/AKT signaling in hepatocellular carcinoma cells. Mol Med Rep. 2017;16(6):8037–44.

72. Li D, Wang G, Jin G, Yao K, Zhao Z, Bie L, et al. Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway. Int J Mol Sci. 2019;43(12):630–40.

73. Zeng Y‑H, Zhou L‑Y, Chen Q‑Y, Li Y, Shao Y, Ren W‑Y, et al. Resveratrol inactivates P38/AKT signaling through upregulating BMP7 in human colon cancer cells. Oncol Rep. 2017;38(1):456–64.

74. Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS, et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res. 2010;70(19):7392–9 (Epub 2010/09/16. eng).

75. Kai L, Samuel SK, Leveson AS. Resveratrol enhances p53 acetylation and apoptosis in prostate cancer by inhibiting MTA1/NuRD complex. Int J Cancer. 2010;126(7):1538–48.

76. Dhar S, Kumar A, Li K, Tzivion G, Levenson AS. Resveratrol regu‑lates PTEN/Akt pathway through inhibition of MTA1/HDAC unit of the NuRD complex in prostate cancer. Biochim Biophys Acta. 2015;1853(2):265–75.

77. Gwak H, Haegeman G, Tsang BK, Song YS. Cancer‑specific inter‑ruption of glucose metabolism by resveratrol is mediated through inhibition of Akt/GLUT1 axis in ovarian cancer cells. Mol Cancer. 2015;14(12):1529–40.

78. Kim TH, Park JH, Woo JS. Resveratrol induces cell death through ROS‑dependent downregulation of Notch1/PTEN signaling in ovarian cancer cells. Mol Med Rep. 2019;19(4):3353–60.

79. Ye M, Tian H, Lin S, Mo J, Li Z, Chen X, et al. Resveratrol inhibits proliferation and promotes apoptosis via the androgen receptor splicing variant 7 and PI3K/AKT signaling pathway in LNCaP prostate cancer cells. Oncol Lett. 2020;20(5):1.

80. Wang Z, Wu L, Tong S, Hu X, Zu X, Li Y, et al. Resveratrol suppresses the epithelial‑to‑mesenchymal transition in PC‑3 cells by down‑regulating the PI3K/AKT signaling pathway. Anim Cells Syst. 2015;19(2):77–85.

81. Palder CJ, Rudak MA, Zhou XC, Wagner WD, Hudson TS, Anders N, et al. A phase I study of muscadine grape skin extract in men with biochemically recurrent prostate cancer: safety, tolerability, and dose determination. Prostate. 2015;75(14):1518–25.

82. Ko JC, Syu JJ, Chen JC, Wang T1, Chang PY, Chen CY, et al. Resveratrol enhances etoposide‑induced cytotoxicity through down‑regulating ERK 1/2 and AKT‑mediated X‑ray repair cross‑complement group 1 (XRCC 1) protein expression in human non‑small‑cell lung cancer cells. Basic Clin Pharmacol Toxicol. 2015;117(6):383–91.
Wang J, Li J, Cao N, Li Z, Han J, Li L. Resveratrol, an activator of SIRT1, induces protective autophagy in non-small-cell lung cancer via inhibiting Akt/mTOR and activating p38-MAPK. Onco Targets Ther. 2018;11:7777.

Rasheduzzaman M, Jeong J-K, Park S-Y. Resveratrol sensitizes lung cancer cell to TRAIL by p35 independent and suppression of Akt/NF-kB signaling. Life Sci. 2018;208:208–20.

Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Cancer Research Third Expert Report on diet, nutrition, physical activity, and cancer: impact and future directions. J Nutr. 2020;150(4):663–71.

Luo H, Umebayashi M, Doi K, Morisaki T, Shirasawa S, Tsunoda T. Resveratrol overcomes cellular resistance to vemurafenib through dephosphorylation of akt in BRAF-mutated melanoma cells. Anticancer Res. 2016;36(7):3585–9.

Wang M, Yu T, Zhu C, Sun H, Qiu Y, Zhu X, et al. Resveratrol triggers protective autophagy through the ceramides/Akt/mTOR pathway involved. Arch Biochem Biophys. 2020;689:108461.

Chen JM, Bai JY, Yang XX. Effect of resveratrol on doxorubicin resistance in breast neoplasms by modulating P38/Akt signaling pathway. IUBMB Life. 2018;70(6):491–500.

Jiao Y, Li H, Liu Y, Guo A, Xu X, Qu X, et al. Resveratrol inhibits the invasion of glioblastoma-initiating cells via down-regulation of the P38/Akt/NF-kB signaling pathway. Nutrients. 2015;7(6):4383–402.

Gong C, Xia H. Resveratrol suppresses melanoma growth by promoting autophagy through inhibiting the P38/Akt/mTOR signaling pathway. Exp Ther Med. 2020;19(3):1878–86.

Hu W, Yang E, Ye J, Han W, Du ZL. Resveratrol protects neuronal cells from isoflurane-induced inflammation and oxidative stress-associated death by attenuating apoptosis via Akt/p38 MAPK signaling. Exp Ther Med. 2018;15(2):1568–73.

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

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

Zhao Y, Tang H, Zeng X, Ye D, Liu J. Resveratrol inhibits proliferation, migration and invasion via Akt and ERK1/2 signaling pathways in renal cell carcinoma cells. Biomed Pharmacother. 2018;98:36–44.

Chang C-H, Lee C-Y, Lu C-C, Tsai F-J, Hsu Y-M, Tsao J-W, et al. Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: a key role of AMPK and Akt/mTOR signaling. Int J Oncol. 2017;50(3):873–82.

Graham RM, Hernandez F, Puerta N, De Angulo G, Webster KA, Vanni S. Resveratrol augments ER stress and the cytotoxic effects of glycolytic inhibition in neuroblastoma by downregulating Akt in a mechanism independent of SIRT1. Exp Mol Med. 2016;48(2):e210.

Zhu W, Qin W, Zhang X, Rottinghaus GE, Chen YC, Kliethermes B, et al. Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer. Nutr Cancer. 2012;64(3):393–400. (Epub 2012/02/16, eng).

Chen X, Hu X, Li Y, Zhu C, Dong X, Zhang R, et al. Resveratrol inhibits Erk1/2-mediated adhesion of cancer cells via activating P2PA–PTEN signaling network. J Cell Physiol. 2019;234(3):2822–36.

Singh AP, Singh R, Verma SS, Rai V, Kaschula CH, Maiti P, et al. Health benefits of resveratrol: evidence from clinical studies. Med Res Rev. 2019;39(5):1851–91. (Epub 2019/02/12, eng).

Berman AY, Motechin RA, Wiesendfeld M, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precis Oncol. 2017. https://doi.org/10.1038/s41698-017-0036-6. (Epub 2017/10/11, eng).

Zortea K, Franco VC, Francesconi LP, Ceresoli KM, Lobato MIR, Belmonte-de-Abreu PS. Resveratrol supplementation in schizophrenia patients: a randomized clinical trial evaluating serum glucose and cardiovascular risk factors. Nutrients. 2016;8(2):73.

Shaito A, Posadino AM, Younes N, Hasan H, Halabi S, Alhababi D, et al. Potential adverse effects of resveratrol: a literature review. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21062084. (Epub 2020/03/22, eng).

Pascual V, Posadino AM, Coissu A, Sanna B, Tadolini B, Gaspa L, et al. Akt downregulation by flavin oxidase-induced ROS generation mediates dose-dependent endothelial cell damage elicited by natural antioxidants. Toxicol Sci. 2010;114(1):101–12. (Epub 2009/12/18, eng).

Posadino AM, Coissu A, Giordo R, Zinellu A, Sotgia S, Vardeu A, et al. Resveratrol alters human endothelial cells redox state and causes mitochondrial-dependent cell death. Food Chem Toxicol. 2015;78:10–6. (Epub 2015/02/07, eng).

Giordo R, Wehbe Z, Posadino AM, Erle GL, Eid AH, Mangoni AA, et al. Disease-associated regulation of non-coding RNAs by resveratrol: molecular insights and therapeutic applications. Front Cell Dev Biol. 2022;10:894305.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions