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Review article

Resveratrol: An overview of its anti-cancer mechanisms

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ABSTRACT

Cancer is one of the leading causes of death worldwide. Chemotherapy and radiotherapy are the conventional primary treatments for cancer patients. However, most of cancer cells develop resistance to both chemotherapy and radiotherapy after a period of treatment, besides their lethal side-effects. This motivated investigators to seek more effective alternatives with fewer side-effects. In the last few years, resveratrol, a natural polyphenolic phytoalexin, has attracted much attention due to its wide biological effects. In this concise review, we highlight the role of resveratrol in the prevention and therapy of cancer with particular focus on colorectal and skin cancer. Also, we discuss the molecular mechanisms underlying its chemopreventive and therapeutic activity. Finally, we highlight the problems associated with the clinical application of resveratrol and how attempts have been made to overcome these drawbacks.

1. Introduction

Cancers are a large family of diseases that involves abnormal cell growth with the potential to invade and spread to other parts of the body. For a normal cell to transform into a cancer cell, the genes that regulate its growth and differentiation must be altered [1]. The majority of cancers, (90–95%), are due to genetic mutations caused by environmental factors, while the remaining 5–10% are due to inherited genes [2].

Resveratrol (3,5,4-trihydroxystilbene) is a naturally-occurring polyphenolic compound which is found in many plants including food items such as grapes (especially skin), blueberries, peanut and red wine [3]. Resveratrol has a wide variety of biological effects including antioxidant, anti-inflammatory, anti-cancer, cardio-protector, neuro-protector and anti-diabetic activities [4]. The chemopreventive and therapeutic actions of resveratrol have been well defined in several recent studies. In this review we highlight the mechanisms by which resveratrol prevent and treats different types of cancer.

2. Pharmacokinetics of resveratrol

Discrepancies between the *in vitro* activities of polyphenol trans-resveratrol present in red wine and the *in vivo* effects in both humans and animals have received much attention. On one hand, many studies have reported a wide variety of biological effects of resveratrol *in vitro*, however, extending such studies to animal models of disease, unfortunately, has not confirmed such effects. This paradox has raised questions about its absorption, bioavailability and metabolism [5]. Recent studies on bioavailability have demonstrated that resveratrol is efficiently absorbed after oral administration but rapidly and extensively metabolized without adverse effects in both rodents and humans. This leads to poor bioavailability of unchanged resveratrol in the systemic circulation. Solaes et al. [6] demonstrated that 50–75% of orally administrated resveratrol is absorbed in rats. In addition, it reaches peak concentrations in the blood and serum of rats 15 min after administration. Moreover, its concentration declines rapidly after reaching a peak, while its metabolites declines much more slowly [6]. Furthermore, it has been reported that trans-resveratrol is completely absorbed from the small intestine and is strongly accumulated in the liver [7].

Resveratrol is metabolized by phase I (oxidation, reduction and hydrolysis) and phase II (glucuronic acid, sulfate and methyl conjugations) immediately after ingestion. Sulfation and glucuronidation of resveratrol occur in the liver and intestinal epithelial cells. The sulfation of resveratrol in human liver is carried out by sulfotransferases (SULTs). While the glucuronidation is carried out on intestinal absorption by uridine 5′-diphospho-glucoronosyl transferases (UGTs). Glucuronidation and sulfation typically reduce permeability of cell to drugs and aid in their excretion. Hydrogenation of the aliphatic double-bond also occurs and is probably mediated by microbial fermentation of trans-resveratrol in the gastrointestinal tract [8].

On the other hand, it has been shown that consumption of 1.0 g of resveratrol affords maximal plasma concentrations of ~0.6 mM in humans [9], but most of the reported *in vitro* studies, particularly those

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relating to cancer, require higher concentrations than this for detectable activity. Nevertheless, some studies have reported that low daily doses of resveratrol have potent chemopreventive effects *in vivo* [10, 11]. Therefore, two hypotheses have been suggested to resolve this conundrum: first, metabolites of resveratrol contribute to the beneficial effects associated with the parent compound; second, conjugates of resveratrol undergo hydrolysis *in vivo* to regenerate the parent compound. Recently, Patel et al. [12] reported that sulfate metabolites are hydrolyzed *in vivo* to liberate resveratrol. But further investigations are needed to test these hypotheses.

3. Resveratrol inhibits cancer

The ability of resveratrol to interfere with all three major stages of carcinogenesis (*i.e.*, initiation, promotion and progression) is well established [13]. Here the therapeutic and chemopreventive roles of resveratrol in colorectal and skin cancers are a particular focus. Skin cancer is the most common cancer in the USA [14] while colorectal cancer (CRC) is the third most common cause of cancer-related death worldwide [15]. Billions of dollars are spent annually on treating CRC and skin cancer so providing an approach to protect against cancer development is urgently needed. The poor bioavailability of resveratrol and its strong accumulation in the colon may make the colon the most convenient target for application; also, the skin is a convenient target through topical application.

3.1. Colorectal cancer

The pathogenesis and development of CRC are multi-step processes orchestrated through complex molecular signaling mechanisms, including mutations in multiple genes, such as proto-oncogenes and tumor suppressor genes [16]. About 95% of CRC cases are sporadic and caused by common dietary and environmental factors [17]. Old age and lifestyle (consumption of high fat diet and red meat, low-fiber in-take, obesity, lack of physical activity, usage of tobacco (smoking), high consumption of alcohol and diabetes mellitus) are the major factors which influence the CRC [15]. In addition, inflammatory bowel disease (IBDs), Ulcerative Colitis (UC) and Crohn's Disease (CD) are important risk factors in CRC which cause chronic inflammation of digestive tract that leads to CRC development. Hereditary syndromes such as the Lynch syndrome (also known as hereditary non-polyposis colorectal cancer - HNPCC), Familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP) and the hamartomatous polyposis syndromes (Peutz–Jeghers, juvenile polyposis, and Cowden disease) are also risk factors in CRC.

3.1.1. Resveratrol protects against CRC

Several lines of evidence have pointed out the ability of resveratrol to protect against CRC. Resveratrol has been reported to protect against the initiation of colon cancer in F344 rats as it significantly reduces the number of aberrant crypt foci with a mechanism involving induction of pro-apoptotic protein Bax in ACF cells and reduction of P21 expression in surrounding mucosa [10]. It has been shown that resveratrol prevents the formation of colon tumors and reduces small intestinal tumors in $Apc^{Min/+}$ mice by downregulation of genes directly involved in cell-cycle progression and cell proliferation (*e.g.*, cyclins D1 and D2) and upregulating several genes involved in the activation of immune cells [18]. Besides, resveratrol inhibits tumor production in a genetically engineered mouse model of sporadic CRC ($APC^{CKO}/Kras^{mut}$) [19]. In this case, resveratrol has been shown to epigenetically downregulate Kras by increasing the expression of miR-96.

3.1.2. Resveratrol as a therapy for CRC

The therapeutic activity of resveratrol against CRC has been demonstrated by many recent studies. Schneider et al. [20] demonstrated that it significantly inhibits the growth of CaCo2 cells and arrests cell cycle at the S/G2 phase transition, suggesting that the accumulation of cells at this transition is associated with the inhibition of ornithine decarboxylase expression by resveratrol. In addition, relatively high concentrations of resveratrol induce apoptosis in HT-29 and WiDr colon cancer cells by downregulating telomerase activity [21]. Furthermore, resveratrol has been shown to inhibit the growth of human colon cancer in ls174t cells, by inducing the pro-apoptotic protein Bax and inhibiting the anti-apoptotic protein bcl-2 [22]. Besides, resveratrol suppresses the growth of human HCT116 CRC cells *via* the Sirt1-dependent inhibition of NFκB [23].

In spite of the wide availability of preclinical data on chemopreventive and therapeutic actions of resveratrol, clinical studies are rare. Nevertheless, the available data indicate that it is tolerable chemopreventive agent, particularly in CRC. Patel et al. [24] reported that the daily oral administration of 0.5–1 g of resveratrol for 8 days in 20 patients with CRC resulted in a 5% reduction of tumor cell proliferation. In addition, a daily dose of 80 g resveratrol-containing freeze-dried grape powder for 14 days in 8 CRC patients resulted in a significant inhabitation of the Wnt signaling pathway in normal colon mucosa while having no effect on colon cancer cells [25]. Further, daily administration of 5 g micronized resveratrol in 9 patients with colon cancer and liver metastasis led to a 39% increase in cleaved caspase-3 [26].

3.2. Skin carcinogenesis

Skin cancer is one of the most common classes of human malignancy. The most common types are the two major non-melanoma skin cancers of keratinocytic origin: basal cell and squamous cell carcinoma. In the USA alone, > 3 million cases of these cancers are estimated to occur annually [27].

3.2.1. Resveratrol protects from the development of skin cancer

The chemopreventive action of resveratrol in skin cancer has been well established by several recent studies. It has been shown to reduce the onset of skin cancer initiated by 7,12-dimethylbenz[*a*]anthracene (DMBA) and promoted by 12-O-tetradecanoylphorbol-13-acetate (TPA) in CD-1 mice [28]. Moreover, it has been reported that resveratrol protects against UVB mediated skin cancer in the hairless SKH-1 mouse [29, 30]. Reagan-Shaw and his colleagues [29] revealed that resveratrol significantly inhibits the induction of epidermal hyperplasia, mediated by multiple UVB *via* a decrease in proliferating cell nuclear antigen and the down regulation of cdk-2, −4, and −6, as well as cyclin-D1 and -D2. Furthermore, resveratrol prevents photo-damage of the skin through induction of p66Shc phosphorylation in HaCaT cells [31].

3.2.2. Resveratrol as a therapy for skin cancer

The therapeutic role of resveratrol in skin cancer is well recognized. It significantly reduces the tumors in skin carcinogenesis initiated by DMBA and promoted by TPA in male Swiss albino mice [32]. Furthermore, it has been suggested that inhibition of the growth of such tumors in these mice by resveratrol is mediated through p53-dependent apoptosis pathway [33]. Moreover, resveratrol inhibits the growth and induced apoptosis of epidermal squamous cancer cells by inactivating of Wnt2 and its downstream genes [34]. Besides, resveratrol reduces the occurrence, volume and weight of tumors in DMBA-induced skin carcinogenesis in male Wistar rats through the induction of cell-cycle arrest followed by apoptosis [35]. Also, resveratrol delays tumor growth in female C57Bl/6 N mice transplanted with B16-BL6 melanoma cells [36]. In addition, it has been suggested that resveratrol induces apoptosis in melanoma cells *via* the STAT3/β-catenin-dependent suppression of survivin [37].

4. Anti-cancer mechanisms of resveratrol

Although the anti-cancer action of resveratrol is well established,

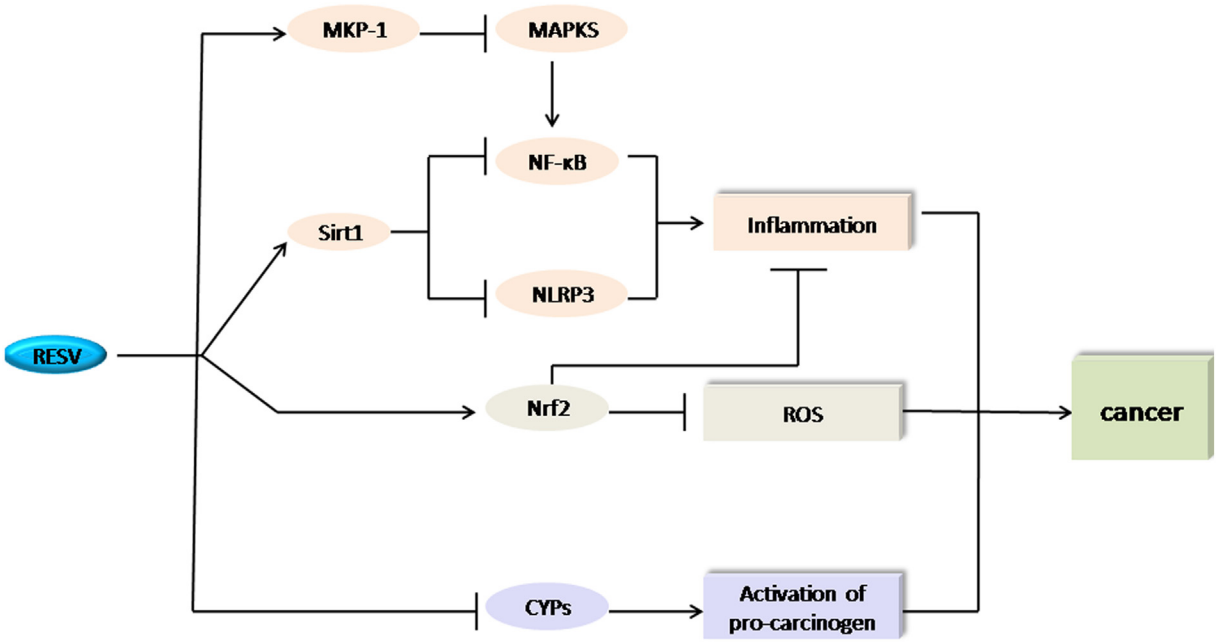

Fig. 1. Schematic diagram of the chemopreventive mechanisms of resveratrol.
Resveratrol suppresses oxidative stress by the Nrf2-dependent activation of anti-oxidant enzymes and the inhibition of activation of pro-carcinogens by down-regulating cytochromes P450. Resveratrol suppresses inflammation by Sirt1-depndent inhibition of NFκB/NLRP3 and its downstream pro-inflammatory molecules, also, through Nrf2 dependent inhibition of pro-inflammatory cytokines and MKP1 dependent downregulation of NFκB.

the exact mechanisms by which it interferes with cancer are not well defined. However, several molecular targets have been suggested to explain its chemopreventive and therapeutic actions.

4.1. Chemopreventive mechanisms of resveratrol

The chemopreventive effect of resveratrol is attributed to its ability to suppress inflammation, eliminate reactive oxygen species, deactivate pro-carcinogens and mimic a state of calorie restriction.

4.1.1. Resveratrol suppress inflammation

Resveratrol has been found to interfere with inflammation, through the regulation of several molecules involved in the initiation of the inflammatory response (Fig. 1).

4.1.1.1. Resveratrol inhibits NLRP3 inflammasome. Recently, it has been pointed out that resveratrol suppresses inflammation by inhibiting the NLRP3 inflammasome. In addition to the NLRP3 protein, this inflammasome contains an adapter protein, apoptosis-associated speck-like protein and procaspase-1 [38]. This inflammasome is a core component of the innate immune system, facilitates the processing of caspase-1, interleukin-1β (IL-1β) and IL-18, and thus amplifies the inflammatory response [39]. It has been reported that Sirt1- dependent autophagy mediates the inhibitory effect of resveratrol on the NLRP3 inflammasome [40]. Resveratrol induces autophagy by upregulating Sirt1 [41], which downregulates the NLRP3 inflammasome by inducing autophagy *via* inhibition of the AKT/mTOR pathway [42].

4.1.1.2. Resveratrol induces mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1). MAP kinase phosphatase-1(MKP-1) is one of the dual-specificity phosphatases that are recognized as key players in inactivating different MAP kinase isoforms [43]. It has been reported that MKP-1 suppress inflammation, by inhibiting the MAP kinases/nuclear factor-kappa B (NF-κB) pathway [44]. Resveratrol suppresses non-typeable *Haemophilus influenzae*-induced inflammation in airway epithelial cells, by inhibiting ERK 1/2 *via* upregulation of MKP-1 [45].

4.1.1.3. Resveratrol induces nuclear factor erythroid 2-related factor 2 (Nrf2). Several investigations have shown that resveratrol induces the expression of Nrf2 and its targeted genes [46, 47]. Resveratrol improves oxidative stress and prevent the progression of periodontitis *via* activation of the Sirt1/AMPK and Nrf2/antioxidant defense pathways in a rat periodontitis model [48].Nrf2 is a transcription factor that induces a battery of cytoprotective genes in response to oxidative/electrophilic stress [49, 50]. Moreover, Nrf2 is known to suppress inflammation, but the mechanism by which it does this is not well defined. However, it has been suggested that elimination of reactive oxygen species mediates its anti-inflammatory effects. Recently, Kobayashi et al. [51] have indicated that Nrf2 suppresses inflammation by binding to the pro-inflammatory cytokine genes IL6 and IL-1B and inhibiting their expression in macrophages. More recently, Nrf2 upregulation by resveratrol in testicular tissues has been found to be mediated by p62-dependent Keap1 degradation [52]. p62 is an adaptor protein that recognizes damaged cellular components and brings them to the autophagosome. Interestingly, Nrf2 also promotes the antioxidant responsive element-driven expression of p62, indicating that autophagy and the Nrf2-mediated antioxidant response work in concert to restore cellular homeostasis.

4.1.1.4. Resveratrol inhibits cyclooxygenase (COX). COX is an enzyme that catalyzes the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid [53]. COX plays a central role in the mediation of inflammation by stimulating prostaglandin biosynthesis. Two isoforms have been identified the constitutively expressed form known as COX-1 and the inducible form COX-2. COX-1 is ubiquitously distributed in several tissue types, while COX-2 is barely detectable under normal physiological conditions but is rapidly induced by pro-inflammatory mediators and mitogenic stimuli. Several recent reports have shown that COX2 is abundant in many types of cancers. In addition, the long term use of COX inhibitors (*e.g.* nonsteroidal anti-inflammatory drugs) significantly reduces the risk of developing many types of cancers [54].

Multiple lines of evidence have demonstrated that the anti-inflammatory and chemopreventive effects of resveratrol are mediated by

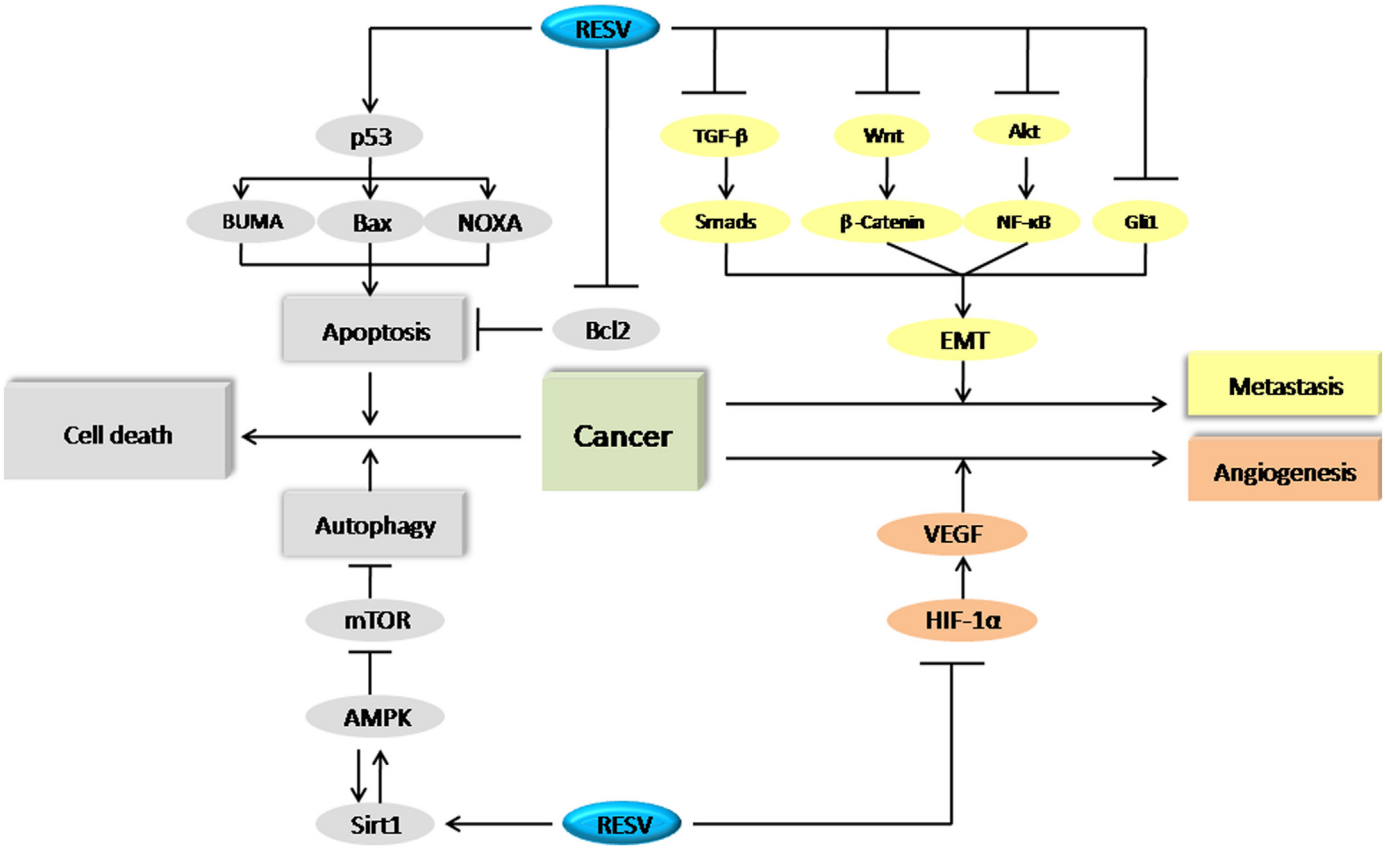

Fig. 2. Schematic diagram of cancer therapeutic mechanisms of resveratrol.
Resveratrol induces cancer cell death by apoptosis through the p53-dependent activation of pro-apoptotic proteins (Bax, NOXA, BUMA). Also, resveratrol induces cancer cell death by autophagy through upregulation of Sirt1 and AMPK. Resveratrol inhibits metastasis by inhibition of the EMT through downregulation of the TGF-β1/Smads, Wnt/β-catenin, PI3K/Akt/NF-κB and Gli1 pathways. Resveratrol inhibits angiogenesis *via* HIF-1α-dependent inhibition of VEGF.

the downregulation of COX-1 and COX-2 expression and activity. Cianciulli et al. [55] reported that resveratrol dose-dependently inhibits the expression of COX-2 in lipopolysaccharide-treated Caco-2 cells, leading to a reduction of PGE2 production. Moreover, resveratrol suppresses *N*-nitrosomethylbenzylamine-induced esophageal tumorigenesis in F344 rats *via* downregulation of COX-2 [56]. Furthermore, it has been suggested that the downregulation of COX-2 by resveratrol is related to NF-κB inhibition [55, 56]. NF-κB plays a key regulatory role in the transcription of pro-inflammatory mediators, including COX-2 [57]. Interestingly, resveratrol interferes with NF-κB activation by suppressing the degradation of IκB and the consequent translocation of the p65 subunit of NFκB from the cytosol to the nucleus [55].

In contrast, it has been suggested that overexpression of COX-2 has an anti-proliferative action through the induction of p53 and p21 [58]. These results suggest that COX-2 plays an important role in p53-dependent apoptosis in cancer cells. Surprisingly, resveratrol has been reported to cause COX-2 accumulation in the nucleus of several human breast cancer, glioma, head and neck, squamous cell cancer, ovarian and prostate cancer cells [59]. Moreover, the specific COX-2 inhibitor, NS398, and an siRNA against COX-2 block the resveratrol-induced p53-dependent apoptosis in cancer cells [60].

4.1.2. Resveratrol regulates drug-metabolic enzymes

One of the major targets that has been suggested to explain the chemopreventive action of resveratrol is inhibition of the metabolic activity of the phase-I enzyme, cytochromes P450 (CYPs). CYPs constitute a superfamily of isoenzymes which are essential for the oxidation of endogenous compounds, drugs, environmental pollutants, dietary chemicals and for the activation of procarcinogens [61]. Piver et al. [62] revealed that resveratrol inhibits CYP3A, CYP1A and CYP2E1 in microsomes from human and rat liver cells. Moreover, it marginally inhibits CYP3A4 and weakly inhibits CYP2C19 [63]. Further, resveratrol abrogates CYP1A1 enzymatic activity induced by Benzo[*a*]pyrene and the subsequent formation of benzo[*a*]pyrene diol epoxide–DNA adducts in Balb-c mice [64].

Another target that is widely recognized to be upregulated by resveratrol is Nrf2. As mentioned above, resveratrol has been found to induce the expression of Nrf2 and Nrf2 target genes [46]. Nrf2 substantially controls xenobiotic metabolism and detoxification. This is based on the ability of Nrf2 to regulate the expression of many of phase-I drug metabolism genes, such as aldo-keto reductases, carbonyl reductases, and aldehyde dehydrogenase 1. Also, many genes involved in phase-II drug metabolism are induced by Nrf2, including glutathione S-transferases, UDP glucuronosyl transferases and UDP-glucuronic acid synthesis enzymes. Besides, induction of efflux transporters, such as multidrug resistance-associated proteins, breast cancer resistant protein, as well as ATP-binding cassette g5 and g8 by Nrf2 has been reported [65].

4.1.3. Resveratrol as a phytoestrogen

Phytoestrogens are biologically-active phenolic compounds of plant origin that structurally mimic the mammalian steroid hormone estradiol (E2. Because of this structural similarity, phytoestrogens can interact with the estrogen receptors ERα or ERβ and interfere with the functions of E2 [66]. Among the phytoestrogens that have been identified as biologically effective compounds, resveratrol stands out as a unique compound. It has been reported that, in absence of 17beta-estradiol, resveratrol acts as an estrogen-agonist and antagonist; while in presence of 17beta-estradiol, it is an anti-estrogen [67]. Resveratrol has a similar affinity toward both ERα and ERβ [68]. ER-α induces cell

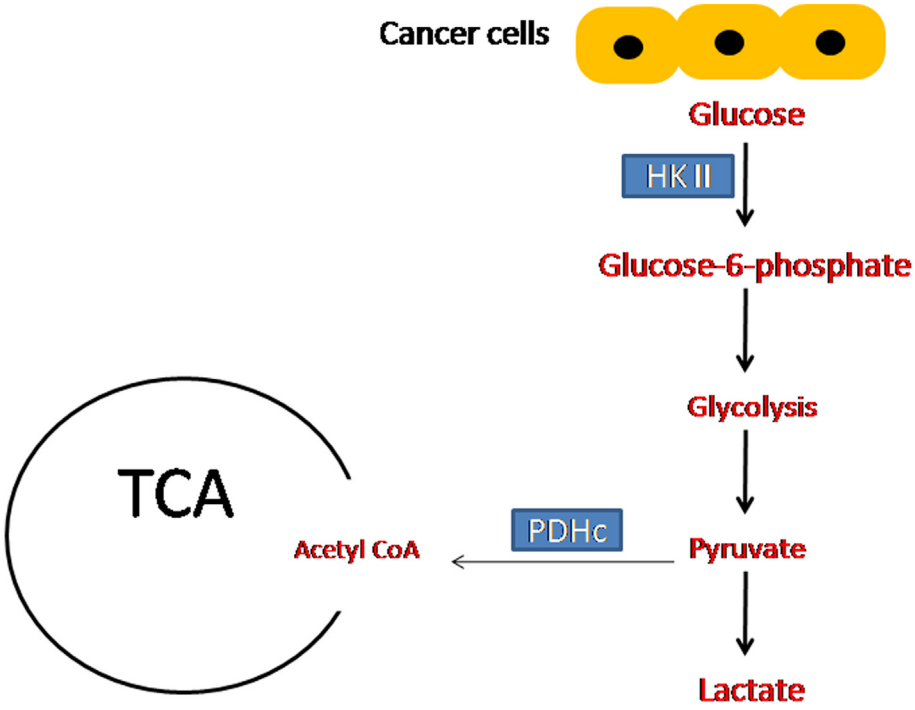

Fig. 3. Schematic diagram illustrating Warburg effect in cancer cells.
Resveratrol has been found to reverse Warburg effect inside cancer cells by activating pyruvate dehydrogenase complex (PDHc). Also, resveratrol inhibits glycolysis inside cancer cells by deactivating hexokinase II (HK II).

proliferation and is elevated in prostate cancer cell lines. On the other hand, ER-β exerts a protective effect by inhibiting the proliferation of cancer cells [69]. According to Bowers et al. [70] resveratrol acts as an antagonist of ER-α but an agonist of ER-β. Interestingly, it has been reported that resveratrol provides protection against prostate cancer through a mechanism involving the upregulation of ERβ expression [71]. Furthermore, resveratrol inhibits the growth of LNCaP cells by inhabiting androgen responsive gene mRNA expression, induced by both androgen and estrogen [72]. In addition, Singh et al. [47] showed that resveratrol inhibits the E2-induced downregulation of Nrf2-downstream anti-oxidant and detoxifying genes in E2-induced mammary tumors resulting in a decreased tumor incidence and increased tumor latency. Furthermore, they suggested that the chemopreventive action of resveratrol in E2-induced mammary tumors is dependent on Nrf2.

4.2. Cancer therapeutic mechanisms of resveratrol

Several mechanisms contribute to the therapeutic action of resveratrol, including its ability to suppress cancer growth, induce cancer cell death by apoptosis and autophagy, as well as inhibit metastasis and angiogenesis (Fig. 2).

4.2.1. Resveratrol induces autophagy

Autophagy is an important response to the cellular environments, and positively regulates cellular processes for survival or death during stress, damage, starvation, aging and pathogen infection [73]. In healthy tissues, autophagy is a process of clearing of damaged, aberrant and long lived organelles and proteins. However, it is a complex process in cancer cells where it can either suppress or induce the growth of cancer cells, depending on the cellular microenvironment [74]. The therapeutic induction of autophagic cell death, through over-stimulation of autophagy, remains another approach for tumor-cell elimination, particularly in apoptosis-defective cells [75]. Resveratrol induces autophagy through the SIRT1/AMPK dependent inhibition of mTOR [41]. Resveratrol has been shown to induce cell death in several cancers by inducing autophagy. Recently, it has been shown that resveratrol-induced A549 cell death was mediated by the process of autophagic cell death *via* Ca(2+)/AMPK-mTOR signaling pathway [76]. Lang et al. [74] reported that resveratrol-induced apoptosis in human ovarian cancer (OVCAR-3) cells is partially mediated through autophagy. Moreover, it has been shown that resveratrol induces autophagy and apoptosis in cisplatin-resistant human oral cancer (CAR) cells, by stimulating the expression of autophagic protein, including Atg5, Atg12, Beclin-1 and LC3-II [73]. Nevertheless, cancer cells have been reported to exploit autophagy for protection against anti-cancer therapy [77]. Resveratrol has been suggested to induce both autophagy and apoptosis in T-cell acute lymphoblastic leukemia (T-ALL) cells, in a dose- and time-dependent manner, but the suppression of autophagy render the T-ALL cells more susceptible to resveratrol-induced apoptosis [78].

Several recent studies have shown that resveratrol protects against the degeneration and damage and enhances the survival of many cells/tissues, including neurons, cardiac tissues and cartilage through its ability to induce autophagy [41, 79–81]. Resveratrol has been reported to protect against spinal cord injury by inducing of autophagy *via* up-regulation of SIRT1/AMPK pathway [41]. Moreover, resveratrol has been suggested to protect against the cardiac tissue damage caused by ischemia and/or reperfusion by stimulating autophagy. In addition, it has been shown that resveratrol protection against doxorubicin-induced heart tissue damage is mediated by stimulating autophagy *via* upregulation of autophagy proteins, including beclin-1, Atg5, p62 and LC3-II, as well as inhibition of mTOR [82]. It is worth noting that limited activation of autophagy is generally considered to be cardioprotective, while excessive autophagy leads to cell death and cardiac atrophy [81].

4.2.2. Resveratrol induces apoptosis

Lines of evidence have demonstrated that resveratrol induces apoptosis in a wide variety of cancer cells, but the underlying mechanism differs greatly among different cancer cell types [83]. Although the precise mechanism of resveratrol-induced apoptosis is still not well defined, the available data indicate that resveratrol triggers several apoptotic pathways. It has been reported that it induces cell-

Table 1
Resveratrol derivatives.

No	Resveratrol derivative	Effect compared to parent resveratrol	IC_{50} (Mm) of resveratrol derivative	IC_{50} (Mm) of resveratrol	Ref
1	2-[[(2-hydroxyphenyl methylene)amino]-phenol	50 times more potent anti-proliferative activity against CRC cell line HCT-116 and glucuronated to a lesser extent	0.6	31	[124]
2	5{(4-hydroxyphenylimino) methyl}benzene-1,2,3-triol	Higher anti-proliferative activity against human breast cancer cell line MCF-7	6.4	>100	[125]
3	5{(4-hydroxyphenylimino)methyl} benzene-1,3-diol	Higher anti-proliferative activity against human breast cancer cell line MCF-7	28.2	>100	[125]
4	Resveratrol tri acetate	Higher cytotoxic activity against acute lymphoblastic leukemia (ALL) cells	3.4	10	[126]
5	Resveratryl triisovalerate	Higher cytotoxic activity against ALL cells	4.9	10	[126]
6	Resveratryl triisobutyrate	Higher cytotoxic activity against ALL cells	5.1	10	[126]
7	(E)-5-(4-Hydroxystyryl) 13phenylene bis(furan-2-carboxylate)	Higher cytotoxicity against human breast cancer cell line MCF-7	42.7	80	[127]
8	(E)-3-Hydroxy-5-(4-hydroxystyryl) phenyl picolinate	Higher cytotoxicity against human breast cancer cell line MCF-7	48.1	80	[127]
9	(E)-3-Hydroxy-5-(4-hydroxystyryl)phenyl thiophene-2-sulfonate	Higher cytotoxicity against human breast cancer cell line MCF-7	43.4	80	[127]
10	3,4,5-tri-O-methyl resveratrol	Seven-fold more active than resveratrol in inhibiting Cyp1A activity	0.03	0.23	[128]
11	3,4,5-tri-O-pivaloyal resveratrol oxide	More potently inhibited induction of iNOS	2.2	18.7	[128]
12	(Z)-3-((E)-2-bromo-4,5-dihydroxystyryl)-N′-hydroxybenzimidamide	More potently inhibited lysine-specific demethylase 1 (LSD1)	0.12	10	[129]
13	(Z)-4-((E)-2-bromo-4,5-dihydroxystyryl)-N′-hydroxybenzimidamide	More potently inhibited LSD1	0.12	10	[129]
14	2,3′,4,4′,5′-pentamethoxy-trans-stilbene	More induction of apoptosis in HT-29 cells	14.7	152.1	[130]
15	5-(6-hydroxy-2-naphthyl)-1,2,3-benzenetriol	More potent tyrosinase inhibitory activity	2.95	55.6	[131]
16	3,5,3′,4′-tetramethoxy *trans*-stilbene	Much more potent inhibitor of mitoxantrone efflux by ABCG2	0.16	ND	[132]

cycle arrest and apoptosis by activating P53; nevertheless, it has also been found to induce apoptosis in P53-mutant tumor cells [84, 85].These findings suggest that resveratrol can induce apoptosis *via* P53-dependent and P53-independent pathways.

On one hand, Kalar et al. [33] suggested that resveratrol-induced apoptosis in mouse skin cancer occurs through the activation of P53 and pro-apoptotic Bax expression with a concomitant reduction of the anti-apoptotic protein Bcl-2. In addition, it has been shown that resveratrol and its methylated derivatives induce apoptosis in rat and human glioma cells by activating P53 [86]. Besides, resveratrol promotes apoptosis in MCF-7cells by inducing P53 activity [87]. Interestingly, resveratrol renders some tumor cells more sensitive to apoptosis by interfering with different signal transduction pathways that regulate p53 activity. It has been reported that resveratrol-induced activation of P53 is mediated by extracellular-signal-regulated protein kinases (ERKs) and P38 in the mouse JB6 epidermal cell line [88]. Moreover, resveratrol sensitizes HepG2 cells to apoptosis by increasing ERK activity and downregulating the expression and activity of AKt, cyclin D1 and Pak1 [89]. In addition, further investigations have shown that resveratrol induces apoptosis in T24 and 5637 cells *via* inhibition of miR-21 expression leading to a decline in Akt activity that results in a decrease in Bcl-2 [90].

On the other hand, Chow et al. [91] have shown that resveratrol-induced apoptosis in human nasopharyngeal carcinoma cells is p53-independent and is mediated *via* the downregulation of the N-terminal truncated isoform of p63.

Apoptosis usually occurs through an extrinsic (death receptor) or an intrinsic (mitochondrial) pathway. Resveratrol-induced apoptosis has been documented to be mostly mediated through the mitochondrial pathway. For example, resveratrol induces apoptosis in lung cancer, bladder cancer, skin cancer, glioma, breast cancer, colon cancer and acute lymphoblastic leukemia cells, *via* the mitochondrial pathway [92, 93].

Nevertheless, the induction of apoptosis by resveratrol through death receptor remains questionable since it does not upregulate the expression of the death receptors [94]. Moreover, blocking these receptors does not suppress the apoptosis induced by resveratrol or its analogues [95, 96]. In contrast, the Fas (first apoptosis signal) death receptor has been reported to mediate resveratrol-induced cell death in colon cancer by redistributing Fas into membrane rafts [94]. Furthermore, resveratrol and some of its derivatives have been found to sensitize some tumor cells to other apoptosis inducers (*e.g.* TNF-related apoptosis-inducing ligand) by inducing death receptors and downregulating cell survival proteins (*e.g.* Survivin) [97, 98]. Survivin is an anti-apoptosis protein and several reports have shown that it is downregulated by resveratrol [99].

Resveratrol induces changes in the Bax/bcl2 ratio, resulting in loss of the mitochondrial transmembrane potential (MTP) with the release of cytochrome C followed by caspase 3 and caspase 9 activation, leading to apoptosis [33]. Remarkably, members of the Bcl-2 family are considered to be potential targets for anti-cancer therapy as they play crucial roles in the regulation of apoptosis [100]. On the contrary, it has been shown that Bax expression is only induced at high doses of resveratrol, while Bax translocation and mitochondria-mediated apoptosis occurs at low doses [101]. These findings suggest the existence of a further mechanism by which resveratrol induces MTP loss.

4.2.3. Resveratrol inhibits angiogenesis

Resveratrol has been shown to inhibit angiogenesis *via* the regulation of VEGF (vascular endothelial growth factor). VEGF is a potent endothelial cell-specific mitogen that plays a crucial role during the process of tumor angiogenesis. It has been demonstrated that resveratrol inhibits VEGF expression in osteosarcoma cells [102]. Moreover, it suppresses VEGF expression in human ovarian cancer cells by downregulating hypoxia-Inducible Factor 1α (HIF-1α) [103]. Interestingly resveratrol not only inhibits Akt- and MAPK-driven HIF-1α basal

expression and its induction by IGF-I, but also it stimulates the proteasomal degradation of HIF-1α [104].

4.2.4. Resveratrol inhibits metastasis

The process of metastasis is complex and involves the spread of carcinoma cells from the primary site to distant sites for tumor formation. The epithelial-to-mesenchymal transition (EMT) is an essential event in the initial step of the metastatic cascade. Resveratrol has been found to interfere with several signaling pathways that regulate the EMT, leading to inhibition of the motility and invasiveness of cancer cells. It has been reported that resveratrol inhibits the liver and lung metastasis of CRC by downregulation the TGF-β1/Smads pathway, which increases the expression of E-cadherin and represses the expression of vimentin [105]. Besides, resveratrol attenuates Wnt/β-catenin signaling by downregulating the long non-coding metastasis-associated lung adenocarcinoma transcript 1, which leads to the inhibition of CRC invasion and metastasis [106]. Furthermore, in Panc-1 pancreatic cancer cells, resveratrol suppresses the metastatic potential *in vitro* by modulating EMT-related factors (E-cadherin, N-cadherin, vimentin, MMP-2, and MMP-9) *via* the PI3K/Akt/NF-κB signaling pathway [107]. Moreover, it has been reported that resveratrol inhibits the invasiveness and metastasis of prostate cancer cells by down-regulating glioma-associated oncogene homolog 1, a transcription factor in the Hedgehog signaling pathway [108]. Recently, it was shown that microRNAs regulate the EMT process, by targeting EMT transcription factors such as ZEB1/2, Snail/Slug, as well as epithelial and mesenchymal markers, including E-cadherin, N-cadherin and vimentin [109]. The growth and metastasis of prostate cancer are reduced by resveratrol through inhibition of Akt/MicroRNA-21 Pathway [110].

4.2.5. Resveratrol reprogram metabolism in cancer cells

Altered metabolism is a universal property of most, if not all, cancer cells. Recently, substantial overlap between metabolic and oncogenic biochemical pathways has been identified, suggesting novel approaches to cancer intervention. Cancer cells must activate or enhance metabolic pathways in order to achieve and sustain high proliferative capacity. These pathways use available nutrients to generate the metabolic precursors for cell anabolism. One of the first identified and most common metabolic change characteristics of cancer cells is altered glucose metabolism or what is called “Warburg effect” [111]. Under normal conditions, Glucose is taken up into the cell by glucose transporters and metabolized to pyruvate in the cytosol through a multi-step process known as glycolysis, which also yields a small amount of ATP. In normal cells, the glycolysis-derived pyruvate is predominantly imported into the mitochondrial matrix where it is oxidized to acetyl coenzyme A (CoA) by the pyruvate dehydrogenase (PDH) complex [112]. Acetyl CoA is then fed into the tricarboxylic acid (TCA) cycle, followed by oxidative phosphorylation (OXPHOS) for high-efficiency ATP generation. Cancer cells, paradoxically, exhibit drastically increased glucose uptake and glycolytic rates and convert much of the glycolysis derived pyruvate into lactate, which is then excreted to the extracellular medium [113]. Moreover, a substantial fraction of glucose carbon, in the form of assorted glycolytic intermediates, is shunted into multiple biosynthetic pathways instead of giving rise to pyruvate [114]. Interestingly, there are several evidences that prove the ability of resveratrol to reprogram metabolism in cancer cells (Fig. 3). Resveratrol has been found to reverse the Warburg effect by enhancing the activity of pyruvate dehydrogenase complex in colon cancer cells [115]. In addition, it has been reported that resveratrol suppresses glycolysis of pancreatic stellate cells *via* downregulation of miR-21 [116]. Therefore, targeting miR-21-mediated glycolysis by resveratrol in tumor stroma may serve as a new strategy for clinical pancreatic ductal adenocarcinoma prevention or treatment. Besides, resveratrol has been found to inhibit the proliferation and induce the apoptosis in ovarian cancer cells *via* inhibiting glycolysis and targeting AMPK/mTOR signaling pathway [117]. Moreover, suppression of non-small cell lung cancer growth by resveratrol has been found to be mediated through hexokinase II – dependent inhibition of glycolysis [118].

5. Recent perspectives

The poor aqueous solubility, low stability and weak bioavailability limit the application of resveratrol. In order to overcome these drawbacks researchers have attempted to develop new derivatives with improved properties for testing as novel therapeutic agents, with emphasis on enhancing their preventive and therapeutic properties. Several derivatives have been described and they have been reported to be superior to the parent compound. The most recently-developed resveratrol derivatives and their effects compared to the parent compound are listed in Table 1.

Another approach that has been tried by researchers to counteract the drawbacks of resveratrol and improve its chemopreventive and therapeutic properties, is to combine it with other compounds and determine whether these combinations show enhanced *in vitro* and *in vivo* antitumor activity. Interestingly, it has been shown that combining resveratrol with piperine significantly improves the bioavailability of resveratrol in C57BL mice [119]. Moreover, the resveratrol and piperine combination sensitizes CT26 and B16F10 cancer cells to apoptosis by ionizing radiation [120]. In addition, it has been shown that resveratrol and curcumin improve the zinc levels and p21 protein expression and decrease the activity of the COX-2 enzyme in benzo[*a*] pyrene-induced lung carcinogenesis in mice [121]. Furthermore, a combination of curcumin, resveratrol and epicatechin gallate named Tricurin has been found to be more potent in killing TC-1 and HeLa cervical cancer cells and results in significant tumor reduction in mice [122]. Also, resveratrol in combination with genistein, provided in the diet, significantly reduces the most severe grade of prostate cancer in the Simian virus 40 T-antigen–targeted probasin promoter rat model, a transgenic model of spontaneously-developing prostate cancer [123].

6. Conclusion

To sum up, resveratrol has been found to interfere with cancer by targeting several molecules and pathways involved in cancer development. However, because of its limited oral bioavailability, its utility as a therapeutic agent in humans remains questionable. This has motivated researchers to develop new derivatives and combinations with improved properties for testing as novel therapeutic agents, with emphasis on enhancing their preventive and therapeutic properties.

Authors contribution to study

ME, XT and YC drafted the MS, XJW, XT and ME edited the MS.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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