Review

Resveratrol addiction: To die or not to die

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Resveratrol, a polyphenol derived from red grapes, berries, and peanuts, has been shown to mediate death of a wide variety of cells. The mechanisms by which resveratrol mediates cell death include necrosis, apoptosis, autophagy, and others. While most studies suggest that resveratrol kills tumor cells selectively, evidence is emerging that certain normal cells such as endothelial cells, lymphocytes, and chondrocytes are vulnerable to resveratrol. Cell killing by this stilbene may be mediated through any of numerous mechanisms that involve activation of mitochondria and of death caspases; upregulation of cyclin-dependent kinase inhibitors, tumor suppressor gene products, or death-inducing cytokines and cytokine receptors; or downregulation of cell survival proteins (survivin, cFLIP, cIAPs, X-linked inhibitor of apoptosis protein (XIAP), bcl-2, bcl-XL) or inhibition of cell survival kinases (*e.g.*, mitogen-activiated protein kinases (MAPKs), AKT/phosphoinositide 3-kinase (PI3K), PKC, EGFR kinase) and survival transcription factors (nuclear factor-kappaB (NF-κB), activating protein 1 (AP-1), HIF-1α, signal transducer and activator of transcription (STAT3)). Induction of any of these pathways by resveratrol leads to cell death. While cell death is a hallmark of resveratrol, this polyphenol also has been linked with suppression of inflammation, arthritis, and cardiovascular diseases and delaying of aging. These attributes of resveratrol are discussed in detail in this review.

Keywords: Apoptosis / Inflammation / Mitochondria / Resveratrol / TNF-alpha

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1 Introduction

Interest in phytopharmaceuticals is accelerating among a growing group of researchers and clinicians as the importance of nutritional factors in many different diseases is being recognized. Support for this interest comes from increasing concern over the efficacy and safety of many conventional therapies, especially in long-term therapies. A large and heterogeneous group of botanicals, nutraceuticals, and herbal drugs have been identified and evaluated during recent years, especially for their activities in cancer, osteoarthritis, and rheumatoid arthritis; these agents include curcumin, tea polyphenols, boswellic acid, withanolides, vitamin E, rosmarinic acid, 6-shoagol from the ginger rhizome, and resveratrol [1–13].

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound found in several plants (Fig. 1). It is composed of two double bonds and exists in two isoforms, *trans*-resveratrol and *cis*-resveratrol. The *trans*-isomer is the more stable form: *trans* to *cis* isomerization is facilitated by UV light and high pH, the *cis* to *trans* conversion is facilitated by visible light, high temperature, or low pH. Resveratrol was first detected in the roots of white hellebore (*Veratrum grandiflorum*) in 1940 [14]. A very high concentration of resveratrol is found in the skin of red grapes [4], but it also occurs in mulberries, peanuts, pines, and root extracts of the weed *Polygonum cuspidatum* [15]. The skin of fresh grapes contains about 50–100 μg/g of resveratrol. The natural function of resveratrol is to protect plants against fungal infections [16], especially against infection with *Botrytis cinerea*. If grapes are infected with this fungus, the concen-

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Abbreviations: AP-1, activating protein 1; **CDK,** cyclin-dependent kinases; **COX,** cyclooxygenase; **ERK,** extracellular signal-regulated kinase; **GJIC,** gap junction intercellular communication; **iNOS,** inducible nitric oxide synthase; **JNK,** c-jun N-terminal kinase; **MAPK,** mitogen-activiated protein kinase; **MMP,** matrix metalloproteinase; **MSK-1,** mitogen- and stress-activated protein kinase 1; **NF-kB,** nuclear factor-kappaB; **PARP,** poly(ADP)ribose polymerase; **ROI,** reactive oxygen intermediates; **ROS,** reactive oxygen species; **SAP,** stress-activated protein; **TNF,** tumor necrosis factor; **TRAIL,** TNF-related apoptosis-inducing ligand; **TPA,** 12-*O*-tetradecanoylphorbol-13-acetate; **Trx,** thioredoxin; **VEGF,** vascular endothelial growth factor

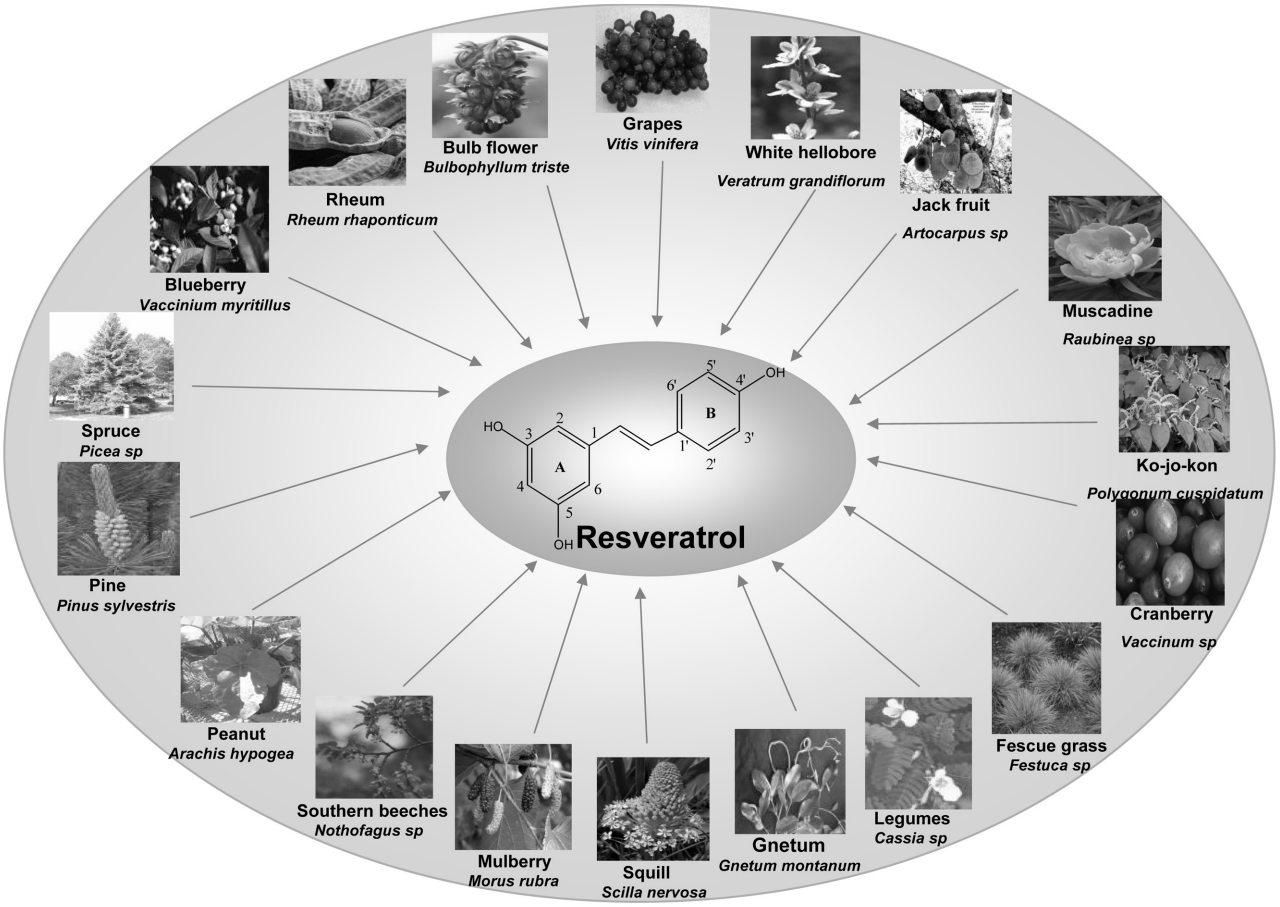

Figure 1. Structure and sources of resveratrol.

tration of resveratrol in the neighboring grapes rises [17]. Environmental stress, such as UV light [18], or heavy metals [19], increases the level of resveratrol in plants.

The great interest to resveratrol has been given over the past decade is mainly due to its anticarcinogenic, anti-inflammatory, and cardioprotective properties (coronary artery protection cumulating in the so called "French paradox") [20–22].

In humans, resveratrol is absorbed mainly in the duodenum; studies in rat intestine indicate that approximately 20% of available resveratrol are absorbed. Most of the resveratrol absorbed in those studies was the conjugated glucuronide form, whereas only very minute amounts of unconjugated resveratrol and resveratrol sulfate were absorbed [23]. Studies in which radiolabeled resveratrol was administered to mice revealed that resveratrol is distributed to all organs. It was detected in the duodenum as well as in the liver and kidney of the mice 1.5 h after administration [24], and remained detectable at these sites for up to 6 h. 3 h after administration, it could also be detected in the lung, spleen, heart, brain, and testis.

Resveratrol is glucuronated in the human liver and sulfated in both the liver and the duodenum [25]. The major derivatives of resveratrol glucuronidation are *trans*-resveratrol-3-*O*-glucuronide, *trans*-resveratrol-4′-*O*-glucuronide, and *trans*-resveratrol-3-*O*-sulfate [26]. Kinetic analysis of resveratrol transformation suggests that, in the liver, glucuronidation is favored over sulfation, with similar rates of reaction. The metabolic modifications of resveratrol can be inhibited by quercetin, a polyphenol also found in wine. Clinical and *in vivo* studies have indicated that free *trans*-resveratrol in plasma is very sparse and short-lived.

Interestingly, several reports suggest that the effects of resveratrol are tissue and/or species specific [27, 28]. Dai *et al*. showed that the stimulatory effect of resveratrol on proliferation of human mesenchymal stem cells is dose dependent. The maximally stimulative resveratrol concentration was 10^{-5} M, whereas a resveratrol concentration of 10^{-4} M turned out to have an inhibitory effect on proliferation [29]. This shows that clinical studies are needed to ascertain the precise dosages needed for specific therapeutic activities.

Resveratrol can be synthesized by treating grape plants with aluminum chloride [30] and irradiating with UV-B and UV-C light [31]. Today, higher yields of resveratrol are achieved through genetic engineering. Design of "functional foods" has led to products containing resveratrol, along with other nutraceuticals or vitamins in many cases.

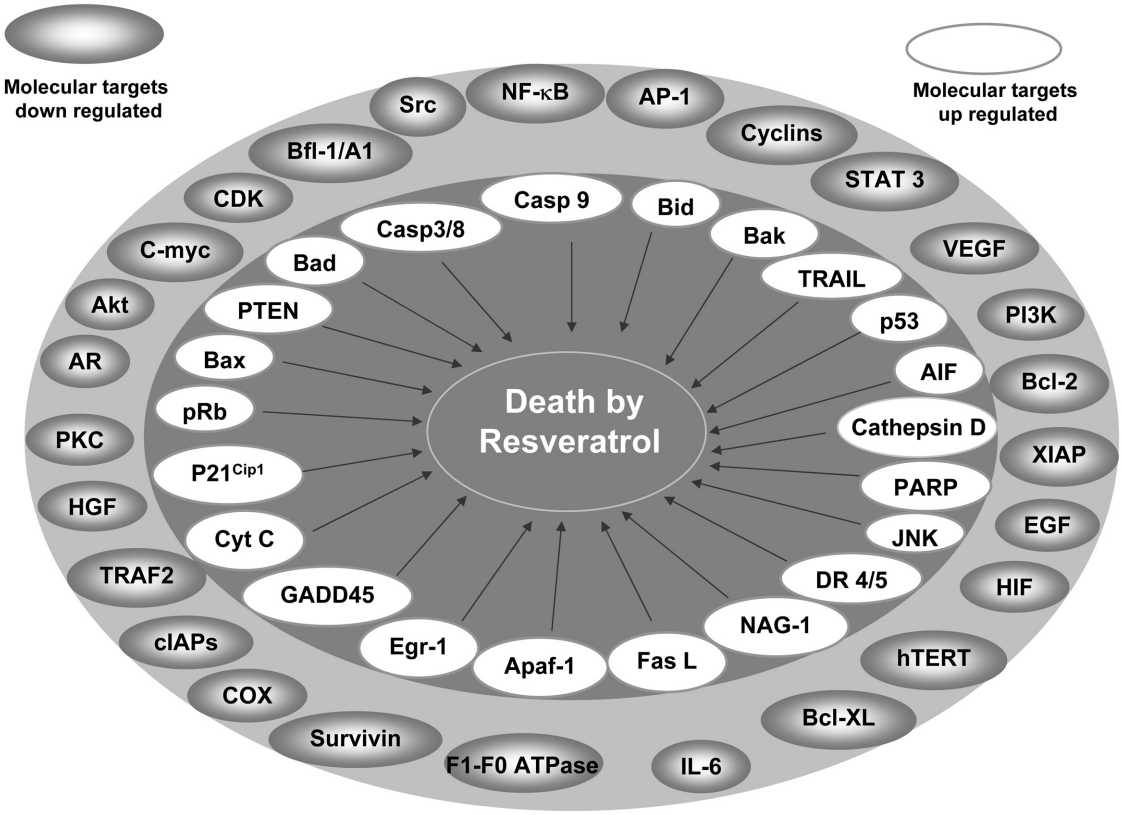

Figure 2. Various molecular targets of resveratrol. AIF, apoptosis-inducing factor; Apaf-1, apoptotic protease activating factor 1; AR, androgen receptor; GADD45, growth arrest and DNA-damage-inducible; hTERT, human telomerase reverse transcriptase; PTEN, phosphatase and tensin homolog; STAT, signal transducers and activators of transcription; TRAF2, TNF receptor associated factor 2; XIAP, X-linked inhibitor of apoptosis protein.

Resveratrol has extensive biological properties, including anticarcinogenic, anti-inflammatory, and estrogenic activities as well as cardiovascular protection, free-radical scavenging, inhibition/induction of apoptosis, and inhibition of platelet aggregation (Table 1). Therefore, resveratrol exhibits numerous different mechanisms of action and targets a great number of intracellular molecules. The various molecular targets of resveratrol are depicted in Fig. 2.

This review aims to give an overview of the action of resveratrol on tumor cells, its anti-inflammatory and cardioprotective actions, and its cartilage-protective effects in osteoarthritis and rheumatoid arthritis and its anti-aging effects.

2 Anticancer effects of resveratrol

There is a growing need for innovative anticancer therapies; ongoing efforts are searching for novel and effective chemopreventive and chemotherapeutic drugs [25, 32, 33]. In the last decade especially, phytopharmaceuticals (*i.e.*, plant-derived natural compounds) have come to the forefront of anticancer therapy research, and many are currently under critical evaluation for their clinical utility and efficacy [34] and to elucidate their effects on cancer-related cell signaling pathways [35, 36]. Resveratrol has been shown to exhibit *in vitro* as well as *in vivo* chemopreventive and chemotherapeutic activities [27, 37, 38]. Many of the signaling pathways involving resveratrol have been evaluated and many of its targets and mechanisms of action have been identified [39]. Indeed, resveratrol has been shown to exhibit chemopreventive and chemotherapeutic activities in all three stages of carcinogenesis (*i.e.*, initiation, promotion, and progression) [40]. These properties have been explained mainly by its activities in cell cycle control and apoptosis induction [41, 40].

Apoptosis especially plays a crucial role in the regulation of tissue homeostasis, and an imbalance between cell death and proliferation may result in tumor formation [42]. Van Ginkel *et al*. [43] concluded that elevated levels of resveratrol lead to tumor regression, associated with widespread tumor cell death, the underlying mechanism of which involves direct activation of the mitochondrial intrinsic apoptotic pathway. Sareen *et al*. showed that resveratrol stimulates apoptosis through activation of this pathway [44].

Table 1. A List of Activities Assigned to Resveratrol

Targets	References
I: Antiproliferative, cytotoxic, cytostatic, and apoptotic effects	
NF-κB	
Blocks activation of NF-κB	[52, 45]
Suppresses phosphorylation and nuclear translocation of the p65 subunit	[52, 54]
Supresses NF-κB-dependent reporter gene transcription through inhibiton of NF-κB, downregulation of COX-2	[52–53, 62]
Activator protein-1 (AP-1)	
Inhibtion of AP-1 through inhibition of c-JNK and MAPK/ERK kinase	[52–53, 59–61]
Reduces AP-1 signaling	[63]
Supression of AP-1 leading to suppression/accumulation of COX-2 (c-JNK and ERK 1/2 involvement)	[62, 64–66, 68, 106]
p53 activation	
Colocalization of p53 with nuclear COX-2 facilitates resveratrol action	[105]
Modulation of p53: transactivation of p53 activity and expression of p53 protein	[71]
Serine phosphorylation of p53 causes apoptosis	[73]
Activation of p53 mediated through ERK 1/2 and p38 activation	[73]
Survivin downregulation	
Downregulation through transcriptional and post-transcriptional mechanisms	[67]
Survivin depletion through p21-mediated cell cycle arrest	[67]
G1 arrest associated with down-regulation of surviving	[67]
Cell cycle targets	
Inhibited proliferation at the S-G2-M phase	[46]
Cell cycle arrest in the S phase	[67]
G1 cell cycle arrest through suppression of AP-1	[52–53, 59–61]
Inhibition of cyclins A and D1 through suppression of AP-1	[52–53, 59–61]
Downregulation of cyclin D1 through inactivation of NF-κB	[54]
Downregulation of CDK 6 through suppression of AP-1	[52–53, 59–61]
p53-independent induction of p21WAF1 through suppression of AP-1	[52–53, 59–61]
p21-mediated cell cycle arrest	[67]
Suppression of AP-1 no influence on cell cycle suppression	[63]
Inhibition of protein tyrosine kinases and protein kinase C through suppression of COX-2 (c-JNK and ERK 1/2 involvement)	[26]
Represses error-prone recombination subpathways	[68]
Apoptosis targets	
Downregulation of Bcl-2	[37, 54–57]
Upregulation of Bax	[37, 54–57]
Accumulation of Bax and Bac	[37, 54, 56–57]
Activation of various caspases	[37, 54, 56–57]
Effect as estrogen analog	
Anticarcinogenic in mammary tumor cells through estrogen modulatory effect	[46, 81–92, 85, 125]
Pro-carcinogenic in *in vivo* model of rats	[83]
Interferes with estrogen-α associated PI3K pathway	[86]
Antagonist of cAMP/kinase-A system	[87]
II: Anti-inflammatory properties	
Downregulation of COX-1/2 through inhibition of NF-κB	[32, 40, 92, 94]
Modifications of eicosanoid synthesis	[40, 94]
Prevention of release of pro-inflammatory mediators	[40, 94]
Inhibition of activated immune cells	[40, 94]
Downregulation of MMP-9 expression through suppressing NF-κB and AP-1	[93]
ROI inhibition	[104, 105]
Induction of p21/WAF1 independently of the p53 pathway	[93]
Inhibition of granulocyte-macrophage colony-stimulating factor release	[32]
Inhibition or induction of ROI cell type and concentration dependent	[97]
Inhibition of lipid peroxidation	[96]
III: Effects in osteoarthritis	
Chondroprotective effect in an *in vivo* osteoarthritis model	[118–119]
Synoviocytes from RA patients *in vitro*: increased caspase-3 and cell proliferation and activation of apoptosis	[120]
Downregulation of caspase-3	[10]
Direct blocking of caspase-3	[13]

Table 1. Continued

Targets	References
Inhibition of PARP cleavage	[13]
Reversing of IL-1ß-induced up-regulation of ROI	[13]
IV: Cardioprotective properties	
GLUT4 expression increased	[100]
Endothelin expression reduced	[100]
VEGF (vascular endothelial growth factor) upregulation	[104, 106]
Trx-1 upregulation	
Nitric oxide/heme oxygenase-1 upregulation	
Manganese-superoxide dismutase activity increased	[104]
Decrease of sICAM and sVCAM	[112]
Inhibition of platelet aggregation	[114]
Inhibition of MAPK avtivation	[87, 113]
Inhibition of MCP-1 (monocyte chemotactic protein-1)	[108]

Prominent, but not yet completely understood, anticarcinogenic mechanisms of resveratrol involve inhibition of activator protein 1 (AP-1) and nuclear factor-kappaB (NF-κB) pathways, modulation of intracellular reactive intermediates, downregulation of survivin, activation of p53, and suppression of cyclooxygenase 2 (COX-2) overexpression [36, 45–47]. In an *in vivo* model of mice genetically predisposed to develop intestinal tumors, resveratrol upregulated several genes that are involved in recruitment and activation of immune cells such as cytotoxic T lymphocyte Ag-4, leukemia inhibitory factor receptor, and monocyte chemotactic protein 3. In inhibition of the carcinogenic process and tumor expansion resveratrol modulate the expression of tumor susceptibility protein TSG101, transforming growth factor-beta (TGF-β), inhibin-β A subunit, and desmocollin 2 [48]. In the following sections we are describing the various mechanisms behind the anticarcinogenic potential of resveratrol.

2.1 Regulation of NF-κB by resveratrol

NF-κB is a prolinflammatory transcription factor involved in control of cell proliferation, differentiation, signaling, and apoptosis, inflammation, stress response, and many other processes. It is thought to play a major role in carcinogenesis and regulate many important signaling pathways involved in tumor promotion [35, 49, 50].

Tumor necrosis factor (TNF) has been shown to mediate tumor initiation, promotion, and metastasis through activation of caspases, NF-κB, AP-1, c-jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and p44/p42 MAPK. It is also a critical component of the immune system, and is required for proper functioning of natural killer cells, T cells, B cells, macrophages, and dendritic cells [51]. It has been shown that resveratrol blocks TNF-induced activation of NF-κB, suppresses TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-κB, and suppresses NF-κB-dependent reporter gene transcription [52].

Banerjee *et al*. reported that resveratrol blocked NF-κB activation induced by 7,12-dimethylbenz(α)anthracene in a mouse model of experimentally induced mammary carcinogenesis, and that this inhibition correlated with downregulation of COX-2 and matrix metalloproteinase (MMP)-9 expression. Treatment of human breast cancer MCF-7 cells with resveratrol suppressed NF-κB activation and inhibited proliferation at the S-G_2-M phase of the cell cycle [45]. Further, resveratrol inhibited the transcriptional activity of NF-κB [53]. In multiple myeloma cells, suppression of constitutively active NF-κB through inhibition of I-κBα kinase and phosphorylation of I-κBα and p65 by resveratrol led to downregulation of various proliferative and antiapoptotic gene products (cyclin D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TNF receptor-associated factor 2 (TRAF2)) and inhibited both the constitutive and the IL 6-induced activation of STAT3 [54]. In implanted primary gastric cancer cells in nude mice, resveratrol-induced apoptosis may be mediated by downregulating expression of the apoptosis-regulated gene Bcl-2 and upregulating the expression of Bax, which is also associated with apoptosis. [55]. In colon/rectal and mammary cancers, resveratrol has been shown to induce apoptosis through activation of various caspases, Bax and Bac accumulation, Fas receptor redistribution, and downregulation of telomerase activity [37, 56, 57]. Further, resveratrol induces caspase-independent apoptosis through Bcl-2 and NF-κB downregulation [58].

2.2 Effects of resveratrol on activator protein 1

AP-1 is a dimeric transcription factor that plays a critical role in carcinogenesis and tumor transformation. In several tumor cell lines, resveratrol inhibited the activation of JNK and its upstream MAPK/extracellular signal-regulated kin-

ase (ERK) kinase (MEK 4). This may explain the mechanism of suppression of AP-1 by resveratrol leading to G_1 cell cycle arrest, which coincides with marked inhibition of G_1 cell cycle-regulatory proteins, including cyclins A and D1 and cyclin-dependent kinase (CDK) 6, and p53-independent induction of p21WAF1 (a CDK inhibitor) [32, 53, 59, 60]. In melanoma cells, however, although AP-1 signaling was reduced, Yang and Meyskens [61] did not observe distinct apoptosis or cell cycle arrest, only phenotypic changes. In HeLa cells, the effects of resveratrol on AP-1 and the MAPK pathway may involve inhibition of both protein tyrosine kinases and protein kinase C [26].

In mouse skin, Kundu *et al*. [62, 63] observed p38 MAPK-mediated activation of AP-1 and attributed it to 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 expression. Indeed, Bhat and Pezzuto [64] observed suppression of COX-1 and -2 enzymatic activities by resveratrol in mouse skin tumors. It has been shown that in phorbol ester-stimulated mammary epithelial cells, resveratrol inhibited activation of protein kinase C and induction of COX-2 promoter activity by c-Jun, suppressed COX-2 expression and prostaglandin synthesis induction, and blocked AP-1 activity [65, 66].

It has been shown, furthermore, that resveratrol induces nuclear accumulation of COX-2 protein in human breast cancer MCF-7 and MDA-MB-231 cell cultures and that this activity was dependent on MAPK/ERK 1/2 and AP-1 [49]. Interestingly, accumulation of nuclear COX-2 in resveratrol-treated cells colocalized with Ser (15)-phosphorylated p53 and with p300, a coactivator for p53-dependent gene expression that facilitates apoptosis in resveratrol-treated breast cancer cells [49].

2.3 Effect of resveratrol on survivin

Survivin is a member of a group of apoptosis-inhibitory proteins; it is expressed at high levels in most human cancers and may facilitate evasion from apoptosis and aberrant mitotic progression. It has been reported that resveratrol can act as a potent sensitizer for anticancer drug-induced apoptosis through cell cycle arrest in the S phase, resulting in induction of apoptosis, preferentially out of S phase, upon subsequent drug treatment. This is mediated by downregulating survivin expression through transcriptional and posttranscriptional mechanisms [67]. Furthermore, Fulda and Debatin observed that resveratrol is a potent sensitizer of tumor cells for TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through p53-independent induction of p21 and p21-mediated cell cycle arrest associated with survivin depletion. Concomitant analysis of cell cycle, survivin expression, and apoptosis revealed that resveratrol-induced G_1 arrest was associated with downregulation of survivin expression and sensitization to TRAIL-induced apoptosis [46]. Resveratrol sensitized various tumor cell lines, but not normal human fibroblasts, to apoptosis induced by death receptor ligation or anticancer drugs. The combined sensitizer (resveratrol)/inducer (*e.g*., TRAIL) strategy may be a novel approach to enhance the efficacy of TRAIL-based therapies in a variety of human cancers [46].

Interestingly, observations regarding the influence of resveratrol on genomic stability have been very ambiguous. A very recent study by Gatz *et al*. showed that resveratrol represses error-prone recombination subpathways by inhibiting both homologous recombination and nonhomologous end joining. These pathways are regulated independently of known growth- and death-regulatory functions of resveratrol [68].

2.4 Effect of resveratrol on activation of p53

p53 is the most commonly mutated tumor suppressor gene, and lack of p53 expression or function is associated with increased risk of tumor formation. In response to genotoxic stress, p53 activates expression of its downstream transcription targets, the products of which are involved in induction of cell cycle arrest, apoptosis, and DNA repair [69, 70].

One of resveratrol's antitumor effects is mediated through its modulation of p53: markedly enhanced apoptosis, transactivation of p53 activity, and expression of p53 protein [71]. Lin *et al*. showed that, in prostate cancer cells, resveratrol-induced serine phosphorylation of p53, causing apoptosis [72]. Furthermore, both ERK 1/2 and p38 kinase-mediated resveratrol-induced activation of p53 and apoptosis through phosphorylation of p53 at serine 15 [73]. Indeed, it was shown that p53 activation of apoptosis in human breast cancer MCF-7 cells can be mediated through intranuclear colocalization of COX-2 with Ser(15)-phosphorylated p53 and p300, a coactivator for p53-dependent gene expression [49]. Although treatment of MCF-7 cells with resveratrol in the presence of 17β-estradiol further enhanced MAPK activation, treatment with 17β-estradiol blocked resveratrol-induced apoptosis by inhibiting resveratrol-stimulated phosphorylation of serines 15, 20, and 392 of p53 and acetylation of p53 [74].

2.5 Effect of resveratrol on other transcription factors

Resveratrol also modulates the expression several other transcription factors that include STAT3 [54], egr-1 [75], Rb, PPAR-γ [76], HIF-1, *etc*. It activates the expression of egr-1, which is downregulated in several types of cancers. In HL-60 cells resveratrol increased egr-1 level through upregulation of the MAPK pathway [75]. Our group showed that this polyphenol is a potent inhibitor of STAT3. Resveratrol inhibited both the constitutive and the IL 6-induced activation of STAT3 in multiple myeloma cells [54]. The inhibition of the STAT3 pathway by this agent was also reported in other cell types [77, 78]. Resveratrol downregulate the expression of pRb in melanoma cells. Vitisin A, a

resveratrol tetramer was also demonstrated to inhibit the phosphorylation of Rb [79]. The expression of PPAR-γ is also decreased by resveratrol in adipocytes [80]. Resveratrol downregulated the expression of HIF-1 expression in various cancer types. All these observations demonstrated that this wine-derived polyphenol modulates the expression of a variety of transcription factors.

2.6 Effect of resveratrol on estrogen receptors

Resveratrol has been shown to act as an anticarcinogenic agent in animal mammary tumor models [45, 81, 82]. It also has been shown that, in prepubertal rats, resveratrol increases the terminal end buds and decreases their differentiation into alveolar buds, which may play a critical role in development of mammary tumors [83].

Resveratrol exhibits an estrogen analog structure and can bind to both α- and β-estrogen receptors [84]. In mammary cancer cells, therefore, apoptotic signaling and modulation of the cell cycle by resveratrol may be due to its estrogen-modulatory effects [64, 82, 83]. Besides its antioxidant and estrogen-modulating activities [85], resveratrol also interferes with an estrogen receptor-α-associated phosphoinositide 3-kinase (PI3K) pathway [86] and acts as an agonist for the cAMP/kinase A system [87].

2.7 Effect of resveratrol on gap junctions

The process of gap junction intercellular communication (GJIC) has been linked to the regulation of development, cellular proliferation, differentiation, and apoptosis [88]. The effect of phytochemicals on GJIC is used as a model to investigate the tumor promotion. In rat epithelial cells the TPA- and DDT-induced inhibition of GJIC was reversed by resveratrol [89]. In HepG2 cells [90] and glioblastoma cells [91] this polyphenol has been shown to increase the GJIC.

3 Regulation of inflammation by resveratrol

Chronic inflammation can lead to cancer, diabetes, and cardiovascular, pulmonary, and neurological diseases. Proinflammatory cytokines that are involved in chronic inflammation are TNF and members of its superfamily, IL-1α, IL-1β, IL-6, IL-8, IL-18, MMP-9, vascular endothelial growth factor (VEGF), COX-2, and 5-lipoxygenase. These genes are regulated mainly by the transcription factor NF-κB; therefore, anti-inflammatory agents that inhibit NF-κB activity may provide new therapies for these diseases [51].

One of the possible mechanisms for the protective activities of resveratrol is downregulation of inflammatory responses [40]. These include inhibition of synthesis as well as release of proinflammatory mediators, modifications of eicosanoid synthesis, inhibition of some activated immune cells, or inhibition of the enzymes, such as COX-1 or COX-2, that are responsible for synthesis of proinflammatory mediators through the inhibitory effect of resveratrol on transcription factors such as NF-κB and AP-1 [92].

It has been shown that the anti-inflammatory effects of resveratrol in TNF-treated vascular smooth muscle cells were mediated through inducing expression of p21/WAF1 independently of the p53 pathway and downregulating MMP-9 expression through the transcription factors NF-κB and AP-1 [93]. In a colitis model, resveratrol reduced COX-2 and NF-κB p65 protein expression, alleviated oxidative events, and returned prostaglandin E2 production to basal levels [94].

Reactive oxygen species (ROS) are known to play a major role in enhancing inflammation through activation and phosphorylation of stress kinases (JNK, ERK, p38) and redox-sensitive transcription factors such as NF-κB and AP-1. In turn, NF-κB and AP-1 regulate expression of genes regulating many proinflammatory mediators (TNF and various ILs). Activation of these proinflammatory mediators through NF-κB is mediated *via* activation of intrinsic histone acetyltransferase activity on coactivator molecules. Acetylation by histone acetyltransferase of specific lysine residues on the *N*-terminal tail of core histones results in uncoiling of the DNA and increased accessibility to transcription factor binding. Deacetylation by histone deacetylase, on the other hand, represses gene transcription by promoting DNA winding, thereby limiting access to transcription factors. ROS are known to inhibit histone deacetylase, resulting in an increased inflammatory reaction and leading eventually to chronic inflammation [95]. In lung epithelial cells, many phytopharmaceuticals are known to play an anti-inflammatory role either through controlling NF-κB activation or through chromatin remodeling *via* modulation of histone deacetylase activity and subsequent inflammatory gene expression [95].

Resveratrol is a potent inhibitor of the dioxygenase activity of lipoxygenases. Lipoxygenases are dioxygenases with peroxidase activity that are involved in synthesis of mediators for inflammatory, atherosclerotic, and carcinogenic processes. Resveratrol can inhibit lipoxygenases through being oxidized by their peroxidase activity. Pinto *et al*. [96] concluded that both resveratrol and its oxidized form can act as inhibitors of the dioxygenase activity of lipoxygenase.

A study by Donnelly *et al*. demonstrated that resveratrol stimulates expression of inducible nitric oxide synthase (iNOS) and nitrite production in human primary airway epithelial cells. Resveratrol also inhibits granulocyte-macrophage colony-stimulating factor release, IL-8 release, and COX-2 expression in these cells. This study demonstrated that resveratrol has nonsteroidal anti-inflammatory activity that may have applications for the treatment of inflammatory diseases [32].

Interestingly, the antioxidant and prooxidant activities of resveratrol appear to be dose and cell type dependent. In human leukemia cells, for example, resveratrol was found to

induce formation of reactive oxygen intermediates (ROI), whereas in prostate cancer cells a dose-dependent decrease in intracellular ROI (in particular, O_2^-) was reported [97].

Inflammation plays a major role in the pathophysiology of several diseases. Resveratrol has been shown to inhibit inflammatory responses through the inhibition of synthesis of various proinflammatory mediators, modulation of prostaglandin synthesis, and through the inhibition of factors such as NF-κB, AP-1, and iNOS. So we can conclude that resveratrol is a novel nonsteroidal anti-inflammatory molecule (NSAID) and possess potential application in the treatment and prevention of various inflammatory diseases.

4 Cardiovascular protection by resveratrol

The first intimations that red wine could have cardioprotective properties were given by epidemiological studies. The so-called "French paradox" was first described by Renaud and de Lorgeril in 1992 [98]; that was followed by an experimental study that first showed the direct protective properties of resveratrol on isolated rat hearts [99].

Resveratrol protects the cardiovascular system in a multidimensional way. The most important effect is inhibition of apoptotic cell death at very low concentrations, thereby providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis, and ventricular arrhythmias. In both acute and chronic disease models, resveratrol-mediated cardioprotection is achieved through a preconditioning effect (the state-of-the-art technique of cardioprotection), rather than a direct effect as found in conventional medicine. The same resveratrol, when administered in higher doses, facilitates apoptotic cell death and behaves as a chemopreventive alternative [92].

In a study by Lekli *et al*., resveratrol improved postischemic cardiac function in Zucker obese rats that received or did not receive 10% glucose solution. The incidence of ventricular fibrillation and infarct size were reduced by 83 and 20%, respectively, in the resveratrol/no glucose group, and by 67 and 16% in the resveratrol/glucose group, compared with obese-control and obese-glucose groups. Resveratrol increased glucose transporter-4 (GLUT-4) expression and reduced endothelin expression and cardiac apoptosis in ischemic-reperfused hearts in the presence or absence of glucose intake [100].

Penumathsa *et al*. [101] concluded that the acute as well as chronic cardioprotection afforded by combination treatment with a statin and resveratrol may be due to proangiogenic, antihyperlipidemic, and antiapoptotic effects and that long-term effects may be caused by increased neovascularization of the infarct zone, leading to less ventricular remodeling.

ROS are pivotal factors in the genesis of heart disease. It is believed that healthy cardiac function requires a fine balance between ROS and endogenous antioxidants. Any disturbance of this balance in favor of ROS may cause an increase in oxidative stress and initiate subcellular changes that can lead to cardiomyopathy and heart failure [102]. A study by Das *et al*. [103] indicated that resveratrol provides cardioprotection by maintaining intracellular redox environments, and that thioredoxin (Trx)-2, the major redox-regulated protein that is primarily responsible for the maintenance of the redox environment inside the heart, is likely to play a role in switching ischemia/reperfusion-induced death signals into survival signals.

Excessive oxidative stress plays an important role in the pathology of diabetes by leading to myocardial ischemia reperfusion injury. Thirunavukkarasu *et al*. [104] investigated whether resveratrol has a direct cardioprotective effect on diabetic myocardium in rats with streptozotocin (65 mg/kg)-induced diabetes. They showed that the mechanisms responsible for the cardioprotective effect of resveratrol in the diabetic myocardium include upregulation of Trx-1, nitric oxide/heme oxygenase 1, and VEGF in addition to increased manganese superoxide dismutase activity and reduced blood glucose level [105]. The regulation of VEGF by resveratrol is a controversial issue. Indeed, Kaga *et al*. [106] showed that resveratrol enhanced myocardial angiogenesis both *in vivo* and *in vitro* by induction of VEGF, which was regulated by Trx-1 and heme oxygenase-1 in rat ischemic myocardium. They found that there was a concentration dependent increase in Trx-1 and HO-1. But how resveratrol induces the expresision of VEGF is not well clear. In a study on human umbilical vein endothelial cells, furthermore, resveratrol was shown to inhibit monocyte chemotactic protein-1 secretion and promoter activity and thus to reduce NF-κB and AP-1 binding activity [107, 108].

Similarly, the cardioprotective activity of resveratrol was demonstrated in studies wherein resveratrol was shown to modulate production of nitric oxide from vascular endothelium [97]. These studies showed that perfused working rat hearts were protected by resveratrol with an increase in iNOS expression. Consistent with this, resveratrol had no cardioprotective properties in iNOS knockout mice [109]. On the other hand, Hung *et al*. found that pretreatment with resveratrol suppressed iNOS induction and enhanced expression of neuronal NOS and endothelial NOS. They concluded that the beneficial effect of resveratrol is mediated through both nitric oxide-dependent and -independent mechanisms [110].

Stress-activated protein (SAP)/MAPK pathway signaling (involving JNK, ERK, and p38 kinase) plays an important role in normal cellular proliferation, differentiation, and programmed cell death. In recent years, considerable advances have been made in our comprehension of the roles of SAP/MAPK signaling in inflammatory disorders such as arthritis and cardiovascular disease and pulmonary and neurogenerative diseases. It has been shown that several natural products such as resveratrol nonspecifically inhibit SAP/MAPK signaling *in vitro*. Resveratrol demonstrates increas-

ing specificity for each of the JNK, ERK, and p38 kinases [111]. El-Mowafy and White [87] showed that short-term treatment of porcine coronary arteries with resveratrol inhibited MAPK activity and reduced phosphorylation of ERK 1/2, JNK-1, and p38 at active sites. Das and Maulik wanted to determine whether, similar to ischemic preconditioning, resveratrol uses MAPKs as upstream signaling targets. They used isolated rat hearts as a model system and found that resveratrol triggers a MAPK signaling pathway involving ERK 1/2 and p38 MAPK, the former using mitogen- and stress-activated protein kinase 1 (MSK-1) as the downstream target and the latter using both MAPKAP kinase 2 and MSK-1 as downstream targets [112]. Furthermore, Das and Maulik described their own recent findings that resveratrol improved postischemic ventricular function and reduced myocardial infarct size. They showed that soluble adhesion molecules such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 were significantly decreased in the group treated with resveratrol [113].

Another mechanism of resveratrol in cardiovascular protection is through the inhibition of platelet aggregation. In a study by Wang *et al*. [114], resveratrol, at concentrations of 10–1000 μmol/L, significantly inhibited platelet aggregation *in vitro* induced by collagen, thrombin, and adenosine 5′-diphosphate in healthy rabbits.

Oxidant-dependent leukocyte infiltration plays a critical role in ischemia/reperfusion-induced tissue injury. While resveratrol attenuated the proinflammatory effects of platelet-activating factor, it did not affect leukotriene B4-induced changes. A study by Shigematsu *et al*. [115] showed that resveratrol prevents leukocyte recruitment and endothelial barrier disruption by inducing a number of superoxide-dependent proinflammatory stimuli, including hypoxanthine and xanthine oxidase and platelet-activating factor. These results emphasize the antioxidant action of resveratrol. Indeed, there is evidence that a novel formulation of resveratrol with emodin, a naturally occurring anthraquinone, is an excellent cardioprotective agent. It is a commercial preparation of resveratrol made from *P. cuspidatum* root extract (Protykin) that function as a free-radical scavenger. Sato *et al*. [116] showed that this preparation protects the heart from ischemia reperfusion injury.

These studies clearly demonstrate that resveratrol protects the heart from I/R injury and also act as pharmacological preconditioning agent.

5 Resveratrol and osteoarthritis

Proinflammatory cytokines such as IL-1β and TNF-α upregulate matrix-degrading enzymes such as MMPs and proinflammatory mediators such as COX-2, leading to cartilage matrix destruction and joint inflammation. This plays an important part in pathogenesis of rheumatoid arthritis and osteoarthritis [9]. COX-2 activation leads to prostaglandin production, mediating inflammation [117]. The classical treatment for osteoarthritis and rheumatoid arthritis are COX inhibitors. However, NSAIDs have well known and severe side effects such as gastric ulcerations (COX-1 inhibitors) and do not inhibit the production of inflammatory stimulating mediators. Thus, current therapies promote cartilage destruction and degeneration. So there is an urgent need for novel, safe, and more effective chemotherapeutic agents for the treatment of osteoarthritis and related arthritic diseases. The major goal of an anti-inflammatory treatment is that on one hand it inhibits COX-2 (and thus prostaglandin production) but on the other hand blocks further ongoing joint degeneration.

A study by Subbaramaiah *et al*. demonstrated that resveratrol has COX-2-inhibitory effects. They induced COX-2 expression in human mammary and oral epithelial cells. The addition of pure resveratrol inhibited COX-2 expression and production of prostaglandin E2 [65]. Martinez and Moreno [28] showed, furthermore, that treatment of mouse macrophages with resveratrol inhibited COX-2 protein expression and suppressed prostaglandin E2 production, while COX-1 protein expression did not change [28]. In contrast, investigations by Jang *et al.* [27] of the effect of resveratrol on phorbol ester-mediated induction of COX-2 in mouse skin detected no influence on induction of COX-2 [27], indicating that the effect of resveratrol depends on tissue and/or species.

In an *in vivo* experimental rabbit inflammatory arthritis model, Elmali *et al*. [118, 119] demonstrated that intra-articular injections of resveratrol had a protective effect on the cartilage. *In vitro* treatment with resveratrol of synoviocytes from rheumatoid arthritis patients demonstrated increased cysteine protease caspase-3 activity, proliferation of synoviocytes, and induction of cell apoptosis [120]. It has been demonstrated *in vitro* that resveratrol, unlike its apoptotic action in tumor cells, has an antiapoptotic effect on chondrocytes that is mediated through inhibition of IL-1β-induced stimulation of caspase-3 and cleavage of the DNA repair enzyme poly (ADP)ribose polymerase (PARP) in human articular chondrocytes [10]. Furthermore, resveratrol directly blocked caspase-3 and subsequent cleavage of PARP and reversed the IL-1β-induced upregulation of ROS in chondrocytes. Results from this study not only show the possible utility of resveratrol in the prevention of osteoarthritis, but also provide interesting results concerning its function as an antioxidant. Moreover, it has been reported that resveratrol induces p53 degradation through an ubiquitin-independent pathway and thus inhibits p53-dependent apoptosis [13].

6 Resveratrol and aging

One of the major aims of aging research is the identification and analysis of compounds that delay the onset of aging and

thus may extend lifespan. Resveratrol has been reported to prolong the lifespan in certain model systems for aging. Resveratrol activates sirtuins (SIRT), an evolutionary conserved family of NAD+ dependent class III histone deacetylases particularly SIRT2 [121]. Resveratrol also alters chromatin structure and transcription and prevents age-related cardiac dysfunction in mice [122]. It also prolongs the lifespan of mice that were fed with a high-calorie diet. Resveratrol increased the insulin sensitivity, decreased the expression of IGF-1 and increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) activity. When examined for the mechanism, it activated FOXO (initially identified in *Caenorhabditis elegans*, which regulates the expression of genes that contribute both to longevity and resistance to various stresses) and insulin-like growth factor-binding protein 1 (IGFBP-1) [122]. Resveratrol can extend lifespan in the yeast *Saccharomyces cerevisiae* [121], the fruit fly *Drosophila melanogaster* [123], the nematode worm *C. elegans* [123], and seasonal fish *Nothobranchius furzeri* [124].

On these bases, resveratrol can be considered as a candidate for an antiaging molecule. But detailed preclinical and clinical investigations are necessary to elucidate the potential of resveratrol as an antiaging molecule.

7 Conclusions

Thus this review demonstrates that based on preclinical studies, resveratrol has the potential for the treatment of various chronic illnesses. In spite of these studies, no systematic clinical trial has yet been done with the pure compound. No data are available on its bioavailability in humans. Such studies should be carried out to realize its full potential.

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