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Resveratrol: An Active Natural Compound in Red Wines for Health

GHULAM MURTAZA[1]*, USMAN LATIF[2], MUHAMMAD NAJAM-UL-HAQ[3], ASHIF SAJJAD[4], SABIHA KARIM[5], MUHAMMAD AKHTAR[6] AND IZHAR HUSSAIN[1]

[1.] Department of Pharmaceutical Sciences, [2.] Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, Pakistan

[3.] Department of Chemistry, Bahauddin Zakariya University, Multan, Pakistan

[4.] Institute of Biochemistry, University of Balochistan, Quetta, Pakistan

[5.] University College of Pharmacy, University of the Punjab, Lahore, Pakistan

[6.] Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur, Bahawalpur, 63100, Pakistan

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ABSTRACT

Phytochemicals found in food have revealed noteworthy roles in treating and managing a large number of human diseases. The structure, source, bioavailability, pharmacokinetics and anti-cancer activity of resveratrol, a bioactive compound present mainly in red wine, are reviewed in this article. Resveratrol, a polyphenol, is a stilbene-type aromatic phytoalexin, which is principally found in red grapes. Numerous physiological activities like antioxidant, anticancer and antiaging activities of resveratrol have been elaborated *in vitro*, in investigational animal models and in human subjects. Studies in humans are still in the preliminary phases and thus, more investigations are required. The anticancer activity of resveratrol is essentially attributable to the genetic variation, moreover, the stimulation of apoptosis through a number of modes, as well as expressions, all causing a reduction in tumor initiation, promotion and progression. No side effects are produced by resveratrol, even when used at elevated quantities. Consequently, resveratrol holds excellent potential to be consumed as an adjunctive or substitute remedy for cancer.

Key words: antioxidant, antiaging, anticancer, resveratrol, wine

INTRODUCTION

The relationship between diet and health is unavoidable because there are certain bioactive compounds in our diet which inhibit the effects and risk of a large number of diseases. When we talk about food, then wine seems to play an essential part with its health promoting properties. The association of health with wine is actually a "French Paradox", observed in the Mediterranean population. The relationship between diet and death by cardiovascular diseases was first studied and published by Renaud *et al.*[(1)]. Myocardial infarction rates were observed to be 40% less in France than the rest of Europe because of proper consumption of wine aside from their diet which is rich in saturated fats. The research on the health effects associated with wine confirms that red wine as a dietary supplement enhances antioxidant activity and reduces oxidative damage and platelet aggregation. In the light of these research studies, it can be suggested that moderate consumption of wine reduces cardiovascular risks[(2-6)].

Including a moderate amount of wine in diet can reduce the risk of cancer, non-hodgkin's lymphoma[(7)], adenocarcinoma of oesophagus[(8-10)] and gastric cardia[(11)]. However, some scientists did not find any relationship between wine and the prevention of different health risks[(12,13)], while some researchers found some negative effects as well[(14)].

Among wines, a higher percentage of antioxidants (polyphenols) is present in red wines and the polyphenols are actually released from the skin and seed of grape during the wine-making process. Almost 1.8 g/L of antioxidants is present in a bottle of red wine, compared to white wine, which contains only 0.2-0.3 g/L of antioxidants[(3)]. The polyphenolic content present in wine depends only on the wine-making process. In the synthesis of white wine, the fermentation is carried out after removing the skin and seeds of the grapes, so white wine contains lesser polyphenols. The antioxidant properties of wines are directly related to the presence of polyphenols. Therefore, white wines show about ten times lesser effects than red wines *in vitro*[(15)]. Apart from resveratrol, white wines contain other antioxidants like tyrosol and hydroxycinnamic acid, but the overall health-promotion activities are lesser than red wines. The studies have lead the

* Author for correspondence. Tel: 00923142082826; Fax: 0092992383441; E-mail: gmdogar356@gmail.com

research attentions to focus on phenolic contents and differentiate its effects than other non-alcoholic constituents[16-19]. The phenolic compounds in red wine also show potential effects in cardiovascular problems and cancer, while experimenting on different animals. In addition, the feed of rats have been supplemented with phenolic compounds, ethanol, or both ethanol and polyphenols in order to differentiate their effects on blood pressure and the heart. It was concluded from these experiments that the polyphenolic extract is most effective in reducing cardiovascular risk[16]. Clifford *et al.* proved that de-alcoholized red wine as a supplement of proper diet has positive effects on tumor onset in transgenic mice[17]. These effects are more pronounced due to the synergy among different phenols: caffeic acid, resveratrol and catechin[18,19]. Apart from resveratrol, the low concentrations of other phenols show very useful activities due to synergy, such as the inhibition of oxidative stress.

A number of papers in the literature can be found in which anticancer properties of resveratrol have been studied[20-26]. Research articles also elucidated the mechanisms that reduce cancer progression. These studies provided evidence that resveratrol can be a promising anti-carcinogenic compound, which exerts potential effects at the initiation, promotion and progression stages of carcinogenesis[21-24,27,28].

This review is focused on the anti-cancer activity of resveratrol, present mainly in wine, along with its structure, availability, pharmacokinetics and possible mechanism as an anti-cancer agent.

LITERATURE SEARCH METHODOLOGY

A broad literature review in English was carried out, employing electronic databases like Medline (1966-2011) and EMBASE (1980-2011). Initially, a sample search was made using terms like “resveratrol” and “activity” together. After that, various terms like “*in vitro*” “antioxidant”, “anti-aging” and “anticancer” were combined with “resveratrol” and “activity” for an advanced search. The literature assessment was carried out by investigating the reference lists of the choosen publications exhibiting innovative investigations to construct an assured review. The publications appropriate for inclusion were the *in vitro* studies presented in the English language. All the literature chosen was corroborated for doubling, which if detected were excluded.

RESULTS AND DISCUSSION

I. *Chemistry and Dietary Sources of Resveratrol*

Resveratrol (3,5,4´-*trans*-trihydroxy stilbene, Figure 1) belongs to the stilbene family and was detected for the first time in *Vitis vinifera* grapevines[29]. It was synthesized in 1992 from leaf tissues by fungal infection or UV light[30]. Resveratrol is a lipophilic off-white powder that is soluble

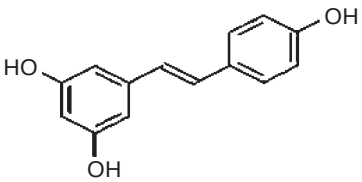

Figure 1. Chemical structure of *trans*-resveratrol.

in ethanol (50 mg/mL) and DMSO (16 mg/mL). Its melting point range is 253-255°C. Its molecular formula and weight are $C_{14}H_{12}O_3$ and 228.25 g/mol, respectively[31]. Due to its poor water solubility and high membrane permeability, it can be classified as a Biopharmaceutical Classification System class-II drug[32,33].

Resveratrol exists in both the *cis*- and *trans*-isomeric forms, where *cis*-resveratrol relatively exists in a larger amount than the *trans*-isomer in Italian red wines[34]. Resveratrol consists of two aromatic rings bridged by ethylene and the carbon atoms of aromatic ring are further attached to three hydroxyl groups. Due to the ethylene group between the aromatic groups, resveratrol exists in *cis*- and *trans*-isomers, and the glucoside derivative of resveratrol is known as piceid. The hydroxyl group of the *trans*-isomer at positions 3 and 4 are very important as it shows antioxidant and apoptotic activities[35]. Resveratrol and other compounds of the stillbene family are present in many plants. We can also get resveratrol from different foods such as grapes, different nuts, berries, dark chocolate and red wine. Among these sources, red wine contains the highest percentage of resveratrol[36]. The concentration of resveratrol is higher in red wine than white wine, because it is present in skin and seeds of grapes, which comes in contact during the fermentation process while making red wine. Due to this reason, the resveratrol concentration in rose wine (0.41 mg/L) is in between red (1.90 mg/L) and white wines (0.13 mg/L)[37-40]. The level of resveratrol in different brands of wine depends on the different varieties of grapes. It also depends on the geographical and environmental conditions. It has been observed in different brands of Italian white wines that the concentration of resveratrol is even lower than the quantification limit[41]. Trebbiano white wine and Sangiovese red wine contain 0.19 mg/L and 0.26 mg/L of resveratrol, respectively[42]. Thus, the level of resveratrol in different commercial red and white wines depends mainly on the wine-making process, and its concentration can be increased by extracting mainly from the skin of grapes[43,44]. However, its exact concentration cannot be predicted in advance because a large number of factors are involved that affects resveratrol synthesis and different concentration ranges have been described in literature[45,46]. The concentration of *trans*-resveratrol content in different foods is shown in Table 1.

In plants, resveratrol is synthesized from phenylalanine and malonyl-CoA[47]. The reaction is catalyzed by three key enzymes and follows the shikimic pathway: phenylalanine ammonium lyase, coenzyme A ligase and stilbene synthase (Figure 2). As the production of these enzymes can

be enhanced by stress[48], the percentage of resveratrol can be increased after exposure to biotic or abiotic stress and microbial attack, which will ultimately enhance the defence mechanism of plants because resveratrol is known to be a phytoalexin[49]. The different forms of phytoalexins depend on the plant sources. The structural forms of phytoalexins are named as hydroxamic acids, di, or sesqui-terpenoids, isoflavonoids, acetylenes, indole alkaloids and stilbenes[50]. The bioactivity of resveratrol in animals is related to its phytoalexinic properties in plants. The percentage of resveratrol in grapes and ultimately in wine depends on several factors such as stress exposure, pathogenic attack[51,52], postharvest treatments with chitosan[53,54] and UVC[55]. The use of transgenic yeast can also increase the level of resveratrol in wines[56]. Such treatments are applied to enhance the level of resveratrol in wine and to ensure the constant and high percentage of this compound over the years, which is highly important according to the commercial point of view to attract the consumers by exploiting nutritional and health terms[58].

Aside from *trans*-resveratrol, other compounds of the stilbene family such as piceid, viniferin and pterostilbene are also present in grapevine leaves as well as in wines prepared from these sources[59-63]. As the percentages of other compounds of stilbene family are very low when compared with resveratrol, there are not many reports on their bioactivities. Stilbene derivatives are also formed from *trans*-resveratrol by different reactions. In susceptile grapevines, resveratrol is produced initially and readily converted to piceid, whereas in resistant varieties, it changes into toxic viniferins by toxic conditions[64].

Table 1. Representative examples of some foods as a source of *trans*-resveratrol

Food	Concentration of *trans*-resveratrol	Reference
Black grapes	0.5 μg/g	Bums *et al.*[11]
Red wine	53 - 1057 μg/100 mL	Bums *et al.*[11]
White wine	0.05 - 1.8 μg/100 mL	Sobolev and Cole[12]
Peanuts (Boiled)	5.1 μg/g	Bums *et al.*[11]
Peanuts butter	0.3 μg/g	Bums *et al.*[11]
Peanuts products (Commercial)	0.018 - 15 μg/g	Sobolev and Cole[12]

II. *Bioavailability and Pharmacokinetics of Resveratrol*

Many studies on the bioavailability of resveratrol in humans and animals (particularly in mice) are available in literature[65-68]. Approximately 70% absorption of orally ingested resveratrol is reported[66]. The high bioavailability of lipophilic resveratrol is perceived on concomitant administration with a fatty diet, but no effect on its bioavailability in humans has been observed. Vitaglione *et al.* administered resveratrol in the form of red wine with meals containing different quantities of fats[69]. In addition, Van Ginkel *et al.* reported that in spite of its low bioavailability, this phytochemical showed cytotoxicity in rats even though there was no detectable concentration of resveratrol in tumor tissues[70].

Due to strong affinity between resveratrol and albumin, an improved distribution and bioavailability of circulating resveratrol has been observed[71]. After oral administration in rats, ^{3}H-labelled *trans*-resveratrol was distributed in the liver, lungs, heart and brain[72]. After ingestion of 4 mL of red wine (each liter of red wine contained 6.5 mg of resveratrol) for 15 days in rats, this phytochemical was found to be distributed in the plasma, bile, feces and urine, as well as in the heart, stomach, intestine, liver and kidneys[73-76]. Similar bioavailability was observed in another study conducted in ten healthy human volunteers, who ingested 300 mL of red wine for 15 days[3]. In contrast, a very low plasma resveratrol level was observed after the intake of 300 mL of white wine for 15 days in another group of ten healthy human volunteers[3].

Walle *et al.* described the liver metabolism of resveratrol and narrated that its phase I metabolism did not occur due to the absence of the required enzymes[77]; however, phase

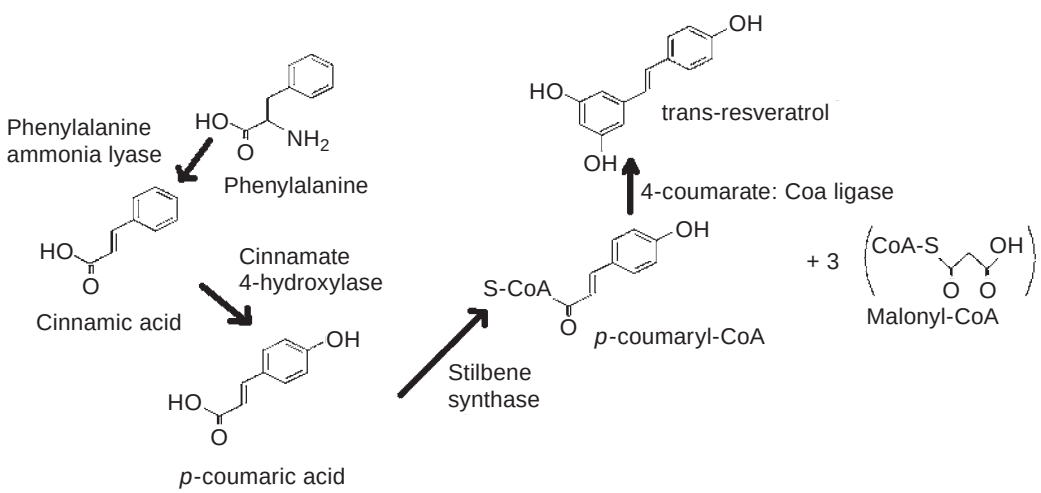

Figure 2. Biosynthesis of *trans*-resveratrol.

II metabolism of resveratrol took place and resulted in its sulfate and glucuronide metabolites[65-68]. Dihydroresveratrol is the metabolite that is produced by the micro-flora of the gastrointestinal tract. After oral administration, the time to reach maximum plasma concentration and half life for resveratrol metabolites is about 30 min and 9.2 h, respectively[77]. The dose of ingested resveratrol affects the plasma levels of resveratrol and its metabolites[78]. After the moderate use of red wine with an identified concentration of resveratrol, five different metabolites including resveratrol monosulphate, dihydroresveratrol monosulphate, dihydroresveratrol and two isomeric forms of resveratrol monoglucuronide were found in the urine samples of volunteers[79]. Six different metabolites, namely *trans*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucoside, free *trans*-resveratrol, resveratrol-40-*O*-glucuronide and *trans*-resveratrol-4-*O*-glucoside, are found in low density lipoprotein samples after the consumption of 250 mL of red wine[80]. Additional experimental data for the therapeutic nature of the metabolites is needed to be investigated due to the elevated level *in vivo* of each metabolite from orally administered resveratrol, compared to resveratrol itself. Resveratrol and its metabolites are discharged *via* urine and feces[68].

Chen *et al.* observed a dose-dependent response of resveratrol[81]. Bertelli proved that resveratrol was effective in cancer and cardiovascular disease in a dose of 5-100 mM and 100 nM - 1 mM, respectively (*in vitro* trials)[82], which also explained how a relatively low dose of resveratrol attained from red wine or other dietary sources could provide therapeutic effect[83]. Bertelli also recommended that the long term intake of red wine in an average amount could result in the absorption of resveratrol in an adequate amount to yield valuable outcomes on human health[82].

Mertens-Talcott and Percival elaborated the potential interactions between resveratrol and other dietary constituents, such as the synergestic effect of resveratrol with both quercetin and ellagic acid for the stimulation of apoptotic cascade in human leukemia cells[84], with ethanol in the under-expression of iNOS[85], with vitamin E in the avoidance of lipid peroxidation[86], with catechin in the defense of PC12 cells against b-amyloid toxicity[87], with nucleoside analogues in the inhibition of HIV1 replication in cultured T lymphocytes[88], and with tyrosol and b-sitoesterol in modulation of LDL oxidative stress and PGE2 synthesis[89]. Goldberg *et al.* investigated the absorptive efficiency, after oral administration to healthy human volunteers, of *trans*-resveratrol, catechin and quercetin in 3 matrices, namely white wine, grape juice and vegetable homogenate[90]. An equivalent absorption of these 3 polyphenols in the different media was observed. De Santi *et al.* reported that quercetin, an essential constituent of red wine, increased the bioavailability of unconjugated resveratrol by inhibiting the sulfation of resveratrol in both the liver and duodenum[76].

Different studies have been carried out to determine resveratrol toxicity. No side effect, even in high dose, has been reported. However, extremely high doses may cause some adverse effects. After the intake for 28 days of resveratrol equivalent to thousand-folds the content in red wine, Juan *et al.* observed no side effects in rats[91]. Williams *et al.* also observed similar outcomes in a 28-day study conducted on rats, where Resvida™ (high purity resveratrol content) produced no side effects at 50, 150 and 500 mg per kg body weight per day[92]. Likewise, in a 90-day study in rats, Resvida™ caused no side effects at the largest tested dose, 700 mg per kg body weight per day.

III. *Antioxidant Property of Resveratrol*

Reactive oxygen intermediates are normally produced in the body by metabolic activities and these substances are removed by the process called detoxification, in which intracellular enzymes like glutathione, catalase, and superoxide dismutase play its role. If they are not removed, abnormal accumulation of oxygen intermediates occurs, resulting in "oxidative stress". In this condition, oxygen intermediates react with biomolecules and cause harmful effects to the body[93], such as the narrowing of blood vessels and heart attack[94].

However, these adverse effects can be circumvented by the antioxidant property of resveratrol as proven by its *in vitro*/*vivo* studies[95-97]. Different experiments were conducted on pigs, rats, and even humans from which we deduced that the risk to peroxidation of biomolecules can be suppressed by taking resveratrol. However, the mechanism by which this compound act against different reactive oxygen intermediates is not clear yet[98].

IV. *Anti-Aging Property of Resveratrol*

Resveratrol exhibits considerable antiaging effects on different species such as *Caenorhabditis elegans*, *Drosophila melanogaster* and *S. cerevisiae*. Moreover, it was observed that the lifespan of shortlived fish was increased by the improvement in sirtuin pathways[99-101]. This compound also has the ability to change the physiology of animals (mice) towards a low-calorie diet, which enhances their endurance and activeness. Baur *et al.* proved that reveratrol reduces the adverse effects of a high calorie diet, decreases insulin-like growth factor-1 levels and improves the number of mitochondria and motor function[98].

V. *Anti-Cancer Property and Mechanisms of Action of Resveratrol against Cancer*

Resveratrol possessed excellent cytotoxic features in a variety of animal models (Table 2). Jang *et al.* first reported on the cytotoxic activity of resveratrol and its mechanism of action[102]. They described the application of resveratrol on mouse skin homing tumor and observed, in each mouse, 98% reduction in the number of skin tumors. Resveratrol was found to be effective at the initiation, promotion and progression stages of cancer (Table 3). They also reported the cyclooxygenase inhibition activity of resveratrol. It is

Table 2. Anti-cancer activity studies of resveratrol *in vitro* and *in vivo*

Model	Dose of resveratrol	Observation	Reference
***In vitro* studies**			
SH-SY5Y, NGP and SK-N-AS cells from human neuroblastoma	50-200 µM resveratrol; Cell treatment for up to 10 days	Induction of apoptosis via over-expression of pro-apoptotic factors	van Ginkal *et al.*[70]
DLD1 and HT29 cells lines from human colorectal cancer	1-100 µM resveratrol; Also co-administered with 1 µM fulvestrant	Over-expression of lysosomal cathepsin D and caspase activation resulting in the apoptosis of cancerous cells	Trincheri *et al.*[106]
Human breast cancer cells (estrogen-positive (MCF-7) and estrogen-negative (MDA-MB-231))	1 µM resveratrol	Decreased cell proliferation in both types of cells	Su *et al.*[113]
S2-013 and CD18 cells from cancerous pancreas of human	25-100 µM resveratrol; Dose administration at 24, 48 and 72 h	Decreased cell proliferation; Significant effect of duration and dose of treatment	Golka *et al.*[121]
RPMI 8226 and U266 cell lines in human multiple myeloma	50 µM resveratrol	Decreased proliferation due to decreased production of anti-apoptic and proliferative factors	Bnhardwaj *et al.*[107]
RPMI 8226, U266, and KM3 cell lines in human multiple myeloma	50-200 µM resveratrol	Induction of apoptosis; Decrease in cell proliferation; Cell cycle arrest	Sun *et al.*[108]
Human colon cancer cells (Etoposide resistant HT-29	50-400 µM resveratrol	Induction of apoptosis via modulation of adenosine monophosphate kinase signaling pathways	Hwang *et al.*[111]
Human T-cell acute lymphoblastic leukemia cells (MOLT-4)	16-128 µM resveratrol	Induction of apoptosis via over-expression of pro-apoptotic factors	Cecchinato *et al.*[112]
Cancerous (estrogen sensitive (LNCaP) and insensitive (PC-3)) and normal cells (PZ-HPV-7) From human prostate gland	Cell treatment with 1-150 µM resveratrol for 12 h to 3 days	Suppression of tumor growth via cell cycle arrest, increase in apoptosis, and decrease in cell proliferation; Significant effect of duration and Dose of treatment	Benitez *et al.*[110]
Human bladder carcinoma (ECV304) cell lines	1-100 µM resveratrol	Induction of apoptosis via modulation of Bcl-2 proteins; Significant effect of duration and dose of treatment	Stocco *et al.*[118]
***In vivo* studies**			
Human neuroblastoma (NGP and SK-N-AS) cells xenografted to mouse	2-50 mg/kg of body weight; administered orally for 35 days	Suppression of tumor growth	Van Ginkel *et al.*[70]
Lewis lung carcinoma cells grafted to mice	5 or 25 mg/kg of body weight; administered intra-peritoneally once daily for 2 weeks	Decrease in metastasis via suppression of angiogenesis	Busquets *et al.*[109]
Breast cancer (MCF-7 and MDA-MB-231) cells grafted to female mice	10 mg/kg of body weight; administered orally for 48 h	Tumor suppression in MDA-MB-231 cells via inactivation of protein kinase B and modulation of Forkhead proteins	Su *et al.*[113]

noteworthy that cyclooxygenase is a risk factor for several cancers. Aggarwal *et al.*, after a series of *in vitro* experiments on tumor cell lines, narrated that cell cycle arrest (anti-proliferation) and apoptosis are the modes of anti-tumor activity of resveratrol[103]. Cell cycle arrest could predominantly be due to the down-regulation of cell cycle proteins[104]. Garvin *et al.* addressed that resveratrol caused an augmentation in apoptosis in *in vivo* tumor models [105]. Multiple modes of apoptosis by resveratrol have been described in literature[72,106-109]. Van Ginkel *et al.*, in mouse xenograft models of human neuroblastoma (SH-SY5Y, NGP and SK-N-AS) cells, observed that resveratrol (at a concentration of 50 mM) provoked the thrashing of mitochondrial membrane potential[70]. This polyphenolic compound induced the liberation of cytochrome C and Smac/Diablo which activated the antecedents (caspase-9 and caspase-3) of the protease-dependent proapoptotic process[70]. Orally administered resveratrol (50 mg/kg body weight/day for 35 days) also suppressed tumor growth[70]. Trincheri *et al.* also observed the inhibition and down-regulation of lysosomal cathepsin D during human colorectal cancer treatment using resveratrol[106]. After 48 h of administering resveratrol (100 mM), the death of human colorectal cancer cells (DLD1 and HT29) was noted[106]. Benitez *et al.* narrated the anti-proliferative activity of

resveratrol at the G0/G1 stage, which subsequently inhibited the cell growth factors in human prostate cancer cell lines[110]. As potential modes of cytotoxicity of resveratrol, the literature also describes some other pathways of apoptosis like (i) raised levels of pro-apoptotic factors such as Bax, p21waf, and p53 in the T-cells homing acute lymphoblastic leukemia[111], (ii) diminished levels of anti-apoptotic factors such as tissue necrosis factor 2, BclxL, Bcl-2, and cyclin D1[107,110], and (iii) deactivation of anti-apoptotic factors such as phosphatidylinositol 3′-kinase[112] as well as the inhibition of serine/threonine protein kinase (STPK) which in return inhibits the Forkhead proteins (also known as transcription factors) in *in vitro* and *in vivo* cancerous cell of human breast[113]. Forkhead proteins are known to activate proapoptotic genes resulting in the programmed death of cells[113]. Moreover, Forkhead proteins are also involved in angiogenesis, the differentiation of cells and DNA repair[114]. Therefore, the mode of cytotoxicity for resveratrol in human may involve Forkhead protein activation. After exposure of estrogen-positive as well as estrogen-negative breast neoplastic cells with resveratrol (10 mg/kg body weight for 48 h), suppression of breast cancer, *in vitro* and in nude mice, was observed[113]. Busquets *et al.* reported that resveratrol, in multiple myeloma cells, could inhibit the nuclear factor (NF)-κB, which is tumorgenic in nature[109]. Resveratrol, in etoposide-resistant cancer cells, also caused programmed cell death by activating the adenosine 5′-monophosphate (AMP) as well as the up-regulation of the protein kinase system. In addition, the release of reactive oxygen species took place, which was also responsible for apoptosis by liberating the cytochrome C from mitochondria. The same mechanism of action for resveratrol was observed in androgen-insensitive prostate cancer cells, i.e. (i) increased release of reactive oxygen species, (ii) inhibition of anti-apoptotic factors, and (iii) upregulation of pro-apoptotic factors such as TNF[115].

Resveratrol, in a mouse model with prostate cancer, stimulated the estrogen receptor-b (a tumor suppressor) and inhibited the growth factors which reduced the proliferation of cells[116]. After administering resveratrol (625 mg/kg of mouse for 196 days), this polyphenolic compound suppressed the development of prostate cancer in transgenic adenocarcinoma mice[116]. On the other hand, Harper *et al.* described the agonistic as well as antagonistic binding of resveratrol with estrogen receptors, which exhibited that resveratrol induced the growth of estrogen-dependent human breast cancer cells[116]. Besides this controversy, there are many experimental studies which described the therapeutic role of resveratrol in breast cancer[117]. Athar *et al.* evaluated the effectiveness of orally administered resveratrol in colorectal cancer by treating the CaCo-2 cells with resveratrol (25 mM) which resulted in 70% growth inhibition[21]. Stocco *et al.* investigated the dose-dependent effect of resveratrol on human bladder carcinoma (ECV304) cell lines during oxidative stress states[118]. Higher doses (>20 μM) of resveratrol induced apoptosis of ECV304 cells *via* increased pro-apoptotic proteins. Provinciali *et al.* elaborated, as a result of food utilization supplemented with resveratrol, a delayed spontaneous growth of mammary tumor in mice and diminished metastasis[119]. Similar results were obtained by La Vecchia and Bosetti, using red wine, but the consumption of red grapes, in breast cancer, showed opposite results[120]. It has been expressed that the risk of prostate cancer can be reduced to half by the intake of one glass of red wine per day. A 60% reduction was observed in prostate cancer incidence in men consuming four glasses of red wine a week[120].

In pancreatic and lung melanomas, resveratrol exhibited antimelanomic activity *in vitro* and in rat models, through the inhibition of cell proliferation[121] and retardation of metastasis[109], respectively. Another report described that resveratrol (5 and 25 mg/kg of body weight/day for 2 weeks) prevented metastasis but could not suppress the development of the tumor *in vivo* mice lung carcinoma cells[109]. This discrepancy exhibited the specific mode of action of resveratrol through different pathways in various cancer cells. The anti-proliferative effect of resveratrol (50 mM), alone and in combination with thalidomide and bortezomib, was studied by Bhardwaj *et al.* in human multiple myeloma cancer cell lines U266 (ATCC TIB-196) and RPMI 8226 (ATCC CCL-155) which were the plasmacytomas of B-cell origin[107].

Sexton *et al.* studied the anti-tumor activity of resveratrol in high dose against uterine cancer cells[122]. They described its mode of action that involved the expression of cyclooxygenase as well as other enzymes which are engaged in prostaglandin synthesis. Harikumar *et al.* investigated the anti-cancer activity of resveratrol (characteristically multitargeted and safe) in combination with gemcitabine (standard drug for pancreatic cancer which is not very efficaceous alone) using the pancreatic cancer xenografts in nude mice[123]. The anti-proliferative activity of resveratrol as well as the apoptotic activity of gemcitabine synergistically suppressed the constitutive activation of NF-κB and expression of carcinogen factors such as bcl-2, bcl-xL, cyclooxygenase-2, cyclin D1 matrix metallopeptidase-9 and vascular endothelial growth factor, resulting in the potentiation of anti-cancer effect of gemcitabine[123]. Wu *et al.* and Bernhaus *et al.* elaborated on the synergistic effect of resveratrol with 5-fluorouracil[124] and gemcitabine[125], respectively.

Table 3. Modes of anti-cancer activity of resveratrol[102,103,109]

No.	Modes of anticancer activity of reveratrol
1	Induction of apoptosis of transformed cells
2	Cell cycle arrest
3	Suppression of angiogenesis
4	Inhibition of invasion and metastasis
5	Sensitizing cancerous cells for chemotherapy induced apoptosis
6	Phase I enzyme inhibition, thus blockage of carcinogen activation
7	Activation of phase II carcinogen detoxifying enzymes via increased anti-oxidant activity
8	Modulation of Forhead proteins

VI. *Approaches to Enhance Resveratrol Bioavailability*

Water solubility, membrane permeability and metabolism of micromolecular drugs play an important role in their oral bioavailability[126,127]. Numerous attempts on enhancing the bioavailability of resveratrol have been documented[126-142]. To stabilize and protect resveratrol, this highly photosensitive drug had been effectively formulated as monodisperse functionalized porous polymeric microspheres[128]. Another researcher successfully employed *saccharomyces cerevisiae* as an encapsulating wall material to prepare yeast-encapsulated resveratrol[129]. To improve the water solubility of resveratrol, various techniques such as the preparation of complexes with β-cyclodextrins[130-133], nanoemulsion[134] and micellar solutions[135] have been successfully used. Some studies involved the development of sustained release and targeted release formulations such as resveratrol-loaded Ca-pectinate beads and Zn-pectinate, microparticles, double-layered ultrafine fibers using polycaprolactone and resveratrol as the outer and inner layers, β-cyclodextrin nanosponges, acoustically active lipospheres, lipid-core nanocapsules, solid lipid nanoparticles, resveratrol incorporated in liposomes, biodegradable nanoparticles and emulsion–liposome blends and emulsions.

Pterostilbene (3′,5′-dimethoxy-4′-hydroxy-*trans*-stilbene), a natural analog of resveratrol, was studied in healthy rats to compare its absolute and relative bioavailabilities to those of resveratrol after single equimolar i.v. doses (resveratrol 10 mg/kg and pterostilbene 11.2 mg/kg) as well as repeated oral administration for 14 days (resveratrol 50 - 150 mg/kg/d and pterostilbene 56 - 168 mg/kg/d). It resulted in a three- to four-times increased bioavailability and total plasma levels of both the parent compound and its metabolites for pterostilbene in comparison with resveratrol[138].

Youn *et al.* reported that piceatannol (3′,5′,3′,4′-tetrahydroxy-*trans*-stilbene), one of the metabolites of resveratrol produced by the action of cytochrome P450 enzyme CYP1B1 on resveratrol, appreciably inhibited experimentally-induced inflammatory injury as well as over-expressed the iNOS in a similar fashion as resveratrol did in mouse colitis[139].

In future, there will be many other opportunities for augmenting resveratrol bioavailablility, such as by inhibiting resveratrol metabolism and prolonging its availability in blood, screening of resveratrol metabolites for their potential bioactivities, synthesizing and consuming of readily bioavailable resveratrol analogs, and applying nanotechnology in resveratrol delivery system development[136]. Johnson *et al.* co-administered resveratrol with piperine, an alkaloid derived from black pepper, *in vivo* for the inhibition of glucuronidation in healthy mice[137]. This study reported an increase in the maximum level of serum resveratrol, the area under the resveratrol concentration curve, and the time to reach maximum level of serum resveratrol by 1544, 229 and 100% after a single oral administration. In current clinical studies, only conventional dosage forms like tablets and capsules[140,141] are evaluated to assess resveratrol bioavailability in humans. Presently, resveratrol-loaded novel drug delivery systems like micro- and nanoparticles are also being studied[141,142].

CONCLUSIONS

Red wine contains many bioactive compounds including resveratrol (0.38 mg/mL of red wine) which can potentially act as anti-oxidant, anti-aging and anti-cancer agents. There are multiple sources and processing techniques for the preparation of wine, due to which this supplementary diet possesses different phytochemicals in various concentrations. The health-promoting features of resveratrol are now apparent. Many research papers are available in literature which described the pharmacokinetics, bioavailability and potential anti-tumor activities of this polyphenol and its mode of cytoprotective effect. These research investigations provided a direction to further explore this emerging therapeutic agent in cancer therapy. However, the research to disclose its chemopreventive effects is in its initial stage and further studies are needed to determine the amount of red wine or resveratrol that should be ingested in 24 h for the protection of an individual against cancers, the type of food that should be avoided or taken in parallel with the consumption of red wine or other resveratrol supplements to resolve bioavailability issues, and the level of activities of the metabolites of resveratrol. There are many other limitations in these studies, including the need for quality dosage forms, variable study designs, lack of information on disease progression and tumor recurrence, short period studies, and small sample sizes. Therefore, it is impracticable to extract unambiguous conclusions on the clinical value of resveratrol in cancer patients. Phase I clinical studies on healthy people are in progress to achieve specific goals like (i) the determination of levels of resveratrol and its metabolites in plasma and excretions, (ii) dose adjustment, and (iii) toxicity studies of resveratrol. Future studies can be focused on the bioavailability enhancement of resveratrol and possible anti-cancer activities of its metabolites as they are found in considerable quantities in biofluids. In addition, other dietary sources of resveratrol like peanuts and berries should also be investigated as potential anticancer therapies. Finally, the future for effective resveratrol delivery depends on the development of novel formulation strategies to augment resveratrol bioavailability.

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