Potential of resveratrol in anticancer and anti-inflammatory therapy

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Phytochemicals present in food have shown significant prospects in the treatment and management of a vast array of human diseases. Resveratrol is a stilbene-type aromatic phytoalexin predominantly found in grapes, peanuts, berries, turmeric, and other food products. Resveratrol has been reported to exhibit several physiological activities including anticancer and anti-inflammatory activities in vitro and in experimental animal models, as well as in humans. Anticancer activity of this compound is mainly due to induction of apoptosis via several pathways, as well as alteration of gene expressions, all leading to a decrease in tumor initiation, promotion, and progression. Resveratrol exhibits anti-inflammatory activity through modulation of enzymes and pathways that produce mediators of inflammation and also induction of programmed cell death in activated immune cells. Resveratrol has been shown to produce no adverse effects, even when consumed at high concentrations. Hence, resveratrol possesses good potential to be used as an adjunctive or alternative therapy for cancer and inflammatory diseases.

INTRODUCTION

Resveratrol, a non-flavonoid polyphenolic antioxidant, is one of the widely studied phytochemicals with demonstrated health potential due to its antioxidant, anticancer, and anti-inflammatory properties.[1–7] Most research conducted on resveratrol in the last two decades elucidates the mechanisms by which resveratrol exerts its activity in reduction of cancer progression, as well as in reduction of inflammation occurrence. Based on these articles, it could be agreed that resveratrol exerts its anti-carcinogenic properties at the initiation, promotion and progression stages of carcinogenesis in various cancer cells.[2–5,8,9] Anti-inflammatory activity of resveratrol occurs through modulation of pathways that produce pro-inflammatory mediators.[6] The aim of this review is to discuss the possible mechanisms through which resveratrol exerts its anticancer and anti-inflammatory activities.

OVERVIEW OF STRUCTURE AND OCCURRENCE OF RESVERATROL

Resveratrol (3,4′,5-trihydroxy-*trans* stilbene) is a compound belonging to the stilbene class of aromatic phytochemicals existing in *cis* and *trans* forms. It is predominantly found in nature in peanuts (*Arachis hypogaea*)[10] and grapes (*Vitis vinifera*).[11–13] Other natural sources of resveratrol include mulberries, blueberries, cranberries, bilberries, turmeric, and hops[14,15] (Table 1). Commercial products of grapes and cranberries, including red wine, also contain high amounts of resveratrol.[13] Resveratrol is liberated from grape skin during commercial wine production. Commercial white wines also contain resveratrol, but at a concentration lower than that found in red wines.[16] The low concentration of resveratrol in white wine is due to processing conditions; white wine is fermented after the grape skin is removed,

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Table 1 **Some dietary sources and concentrations of *trans*- and *cis*-resveratrol.**

| Dietary source*	*trans*-Resveratrol (µg/g)	*cis*-Resveratrol (µg/g)	Reference
Peanut (boiled)	5.1	–	Burns et al. (2002)[11]
Peanut butter	0.3	–	Burns et al. (2002)[11]
Commercial peanut products	0.018–15	–	Sobolev and Cole, (1999)[12]
Black grapes	0.5	–	Burns et al. (2002)[12]
Red wines	53–1057[†]	45–746[†]	Wang et al. (2002)[13]
			Burns et al. (2002)[11]

* For a more detailed list of resveratrol content in various dietary sources, see Baur and Sinclair (2006)[15].

[†] Concentration expressed as µg/100 mL.

whereas red wine is fermented with the grape skin, which allows absorption of resveratrol into the wine.[17] Buiarelli et al.[16] reported that Italian white wines produced from different varieties of grape contain the different forms of resveratrol in amounts lower than the limits of quantification as detected using the HPLC-tandem mass spectrometry method of analysis. However, Mercolini et al.[17] have reported that commercial Trebbiano white wines contain about 0.19 mg resveratrol/L whereas Sangiovese red wines contain 0.26 mg resveratol/L when analyzed using the solid-phase extraction HPLC-F method.[17] Thus, the differences between the resveratrol contents of commercial red and white wines may depend on the brand of wine, wine-making technologies, and the method of detection and quantification of resveratrol. The chemical structure of resveratrol is also found in the form of a *cis* isomer, which is found in relatively lower amounts in wine than the *trans* isomer. However, Wang et al.[13] reported that *cis*-resveratrol predominates over the *trans* isomer in Italian red wines. Resveratrol comprises of two aromatic rings joined together by an ethylene bridge. The aromatic rings also possess three hydroxyl groups attached to their carbon atoms, as observed in most polyphenolic compounds. Both the *trans* and *cis* isomers of resveratrol also exist in the form of their glycosides; the glucoside derivative of resveratrol is known as piceid (Figure 1). Resveratrol is biosynthesized in plants from a coumaryl derivative and malonyl-CoA in a reaction catalyzed by stilbene synthase.[18] Resveratrol is considered as a phytoalexin, which represents an important part of the defense mechanisms of plants. Phytoalexins are a group of low molecular weight secondary metabolites of plants biosynthesized in response to different kinds of environmental stress and microbial attack.[19] Depending on the plant sources, phytoalexins could exist in different structural forms, which include cyclic hydroxamic acids, diterpenoids, sesquiterpenoids, isoflavonoids, polyacetylenes, indole alkaloids and stilbenes.[19] The phytoalexinic properties of resveratrol in plants may explain the bioactivity associated with this molecule in animals.

The discovery of resveratrol as a bioactive phytochemical in red wine followed the report of the "French Paradox" and an attempt to solve the puzzle posed by the discovery that, in France, individuals who consumed a diet rich in saturated fat did not show a high risk of developing cardiovascular disease.[20] This observation was attributed to red wine consumption within that population,[20] and the polyphenolic components of red wine were considered as the active agents.[21] Moreover, an article showed the chemotherapeutic potentials of resveratrol in the treatment of cancer and inflammation.[22] The authors suggested that, since resveratrol is found in the human diet, it would be worthy of further investigation as a dietary source of a cancer chemopreventive agent in humans.[22] Since the past decade, several scientific and a few clinical studies have been conducted in a bid to solve the puzzle behind the bioactivity associated with this structurally simple molecule. Moreover, analysis of
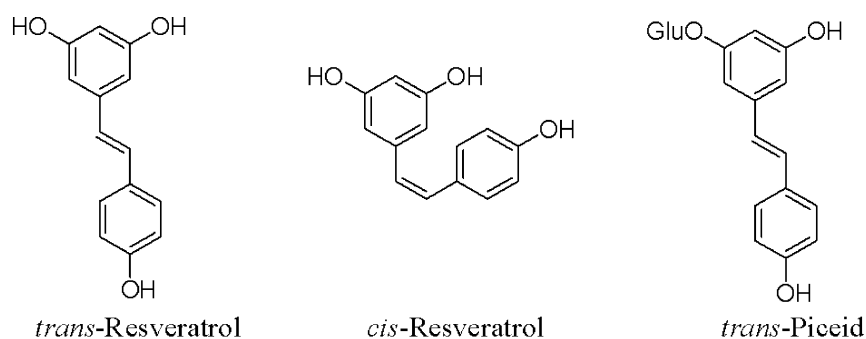
Figure 1 **Chemical structures of *trans* and *cis* isomers of resveratrol and piceid.**
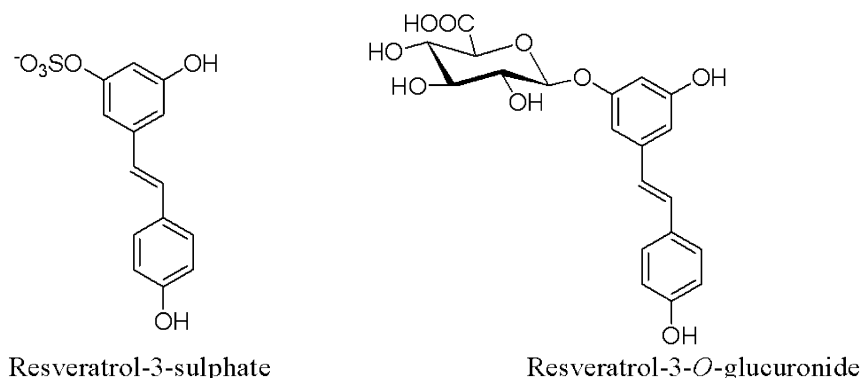
Figure 2 **Chemical structures of major rat and human metabolites of resveratrol.**

the anticarcinogenic properties of four polyphenols in red wine suggested that resveratrol may be the most effective anticancer agent in red wine after oral administration in humans.[23]

BIOAVAILABILITY AND METABOLISM OF RESVERATROL

Bioavailability and metabolism of resveratrol have been widely studied; in rats and in humans its efficacy depends on its absorption and metabolism. In rats, resveratrol has been detected in the feces, urine, bile, and plasma as well as in kidneys, stomach, intestine, and liver, following oral administration.[23–26] Resveratrol is, therefore, efficiently absorbed in rats[24–26] and in humans[22,27] after oral administration, and these results reveal wide tissue targeting of this molecule. As with other polyphenolic xenobiotics, resveratrol is metabolized by liver phase II enzymes leading to the production of mostly its glucoronide and sulphate metabolites (Figure 2).[23–26] These metabolites include *trans*-resveratrol-3-O-glucuronide, *trans*-resveratrol-3-sulfate, *trans*-resveratrol-4′-sulphate, *trans*-resveratrol-3,5-disulfate, *trans*-resveratrol-3,4′-disulphate, and *trans*-resveratrol-3,4′,5-trisulphate.[23–26] As the parent structure has been discovered to remain intact in some target tissues,[26] it could be that the phase I enzymes do not play any significant role in resveratrol metabolism. While most authors reported low bioavailability of resveratrol in plasma and various tissues in rats,[24,27] Abd El-Mohsen et al.[28] showed that, in rats, the ^{3}H-labelled *trans*-resveratrol was the main form identified in the liver, lungs, heart, and brain following oral administration.

Due to the lipophilicity of resveratrol, it would be expected that resveratrol consumption with a diet rich in lipids would increase its absorption and bioavailability. However, in a human study in which resveratrol was administered with meals containing varying amounts of lipids, Vitaglione et al.[29] reported that the bioavailability of *trans*-resveratrol consumed in red wine in humans was independent of the lipid content of the meal. Despite its low bioavailability, resveratrol has been reported to exhibit its anticancer activity in rats even though there was no observed accumulation of this phytochemical in tumor tissues, where activity is needed.[30] After biotransformation by detoxification enzymes, resveratrol and its conjugates are excreted in the urine and feces.[26]

ANTICANCER ACTIVITIES OF RESVERATROL

Resveratrol has shown potential anticancer activity in various cancers at the initiation, promotion, and progression stages (Table 2).[22] Resveratrol has been shown to induce cell death in mouse xenograft models of human neuroblastoma (SH-SY5Y, NGP, and SK-N-AS) cells at 50 µM.[30] Moreover, resveratrol induced cell death in human colorectal cancer cells (DLD1 and HT29) upon 48 h of exposure to 100 µM of resveratrol.[31] Inhibition of breast cancer progression by resveratrol has been reported in both estrogen-positive (MCF-7) and estrogen-negative (MDA-MB-231) breast cancer cells when treated with 1 µM resveratrol in vitro and in nude mice inoculated with any of these cell lines, resveratrol reduced the cancer progression when administered with 10 mg per kg body weight (BW) for 2 days.[32]

Resveratrol also possesses a strong anticancer property in various animal models (Table 3). It has been reported that administration of 625 mg of resveratrol per kg diet for 28 weeks suppresses the progression of prostate cancer in transgenic adenocarcinoma mouse prostate (TRAMP) mice.[41] The tumor growth was also inhibited in rats by oral administration of 50 mg per kg BW per day of resveratrol for 5 weeks.[30] In addition, this polyphenolic compound showed anticancer activity in pancreatic and lung cancers by inhibiting cell proliferation in vitro[33] and by reducing metastatic growth in rat models,[40] respectively. However, Busquets et al.,[40] in their experiments with C57B1/6 mice inoculated intramuscularly with

Table 2 **Anticancer properties of resveratrol in vitro.**

Reference	Model	Dose	Outcome/mechanism
van Ginkel et al. (2007)[30]	Human neuroblastoma (SH-SY5Y, NGP, and SK-N-AS) cells	50–200 µmol/L resveratrol; cells were treated for up to 10 days	Viability of cancer cells decreased by 85–90% after 5 days of treatment; IC_{50} values of 70–120 µmol/L in the different cells after 48 h of treatment; induced loss of mitochondrial potential leading to activation of proapoptotic caspases and subsequently programmed cell death
Trincheri et al. (2007)[31]	Human colorectal cancer (DLD1 and HT29) cells	1–100 µM resveratrol in the absence or presence of 1 µM fulvestrant	Induced cancer cell death; anticancer activity not mediated through estrogen receptors; proposed to be mediated by upregulation of lysosomal cathepsin D expression and caspase activation, resulting in apoptosis
Su et al. (2007)[32]	Estrogen-positive (MCF-7) and estrogen-negative (MDA-MB-231) breast cancer cells	1 µM resveratrol	Reduced proliferation in both estrogen-positive and estrogen-negative human breast adenocarcinoma
Golka et al. (2007)[33]	Human pancreatic cancer (S2-013 and CD18) cells	25–100 µM resveratrol treatment at 24, 48, and 72 h	Inhibited cell proliferation in both cancer cells at 100 µM; Induced time- and concentration-dependent transcriptional upregulation of macrophage inhibitory cytokine-1 (MIC-1), which possesses antitumorogenic activity
Bhardwaj et al. (2007)[34]	Human multiple myeloma (U266 and RPMI 8226) cells	50 µM resveratrol	Inhibited proliferation in chemoresistant and chemosensitive cells by decreasing proliferative and antiapoptotic factors; mediated through suppression of NF-κB via IKK inhibition; potentiated the apoptotic effects of bortezomib and thalidomide; induced a G_1 cell cycle arrest
Tang et al. (2007)[35]	Human breast cancer (MCF-7 and MDA-MB-231) cells	30 µM resveratrol	Induced nuclear accumulation of COX-2 in MCF-7 cells, which associates with and facilitates the p53-dependent proapoptotic activity
Sun et al. (2006)[36]	Human multiple myeloma (RPMI 8226, U266, and KM3) cells	50–200 µM resveratrol	Suppressed cell proliferation with IC_{50} values of 131–187 µM after 24 h; induced cell cycle arrest at G_1 and S phases; inhibited expression of NF-κB and downregulation of its antiapoptotic gene products; induced apoptosis
Hwang et al. (2007)[37]	Etoposide-resistant HT-29 human colon cancer cells	50–400 µM resveratrol	Induced cell growth inhibition with etoposide in etoposide-resistant cancer cells; induced apoptosis with etoposide by modulation of AMP kinase signalling pathway and ROS production
Cecchinato et al. (2007)[38]	MOLT-4 human T-cell acute lymphoblastic leukemia cells	16–128 µM resveratrol	Induced a decrease in cell viability through induction of apoptosis by increasing proapoptotic factors Bax, p53, p21waf, and modulated the p53 and PI3K/Akt-mediated apoptosis pathway
Benitez et al. (2007)[39]	Human prostrate-derived estrogen-sensitive LNCaP and estrogen-insensitive PC-3 cancer cell lines, and PZ-HPV-7 normal cells	1–150 µM resveratrol; cells treated for 12–72 h	Induced a dose- and time-dependent decrease in cancer cell proliferation and an increase in caspase-dependent apoptosis; induced cell cycle arrest at G_0/G_1 phase; reduced the expression of cancer cell growth factors; anticancer activity via different mechanisms in the two cell types

Abbreviations: Akt, protein kinase B; AMP, adenosine 5′-monophosphate; PI3K, phosphatidylinositol 3′-kinase; ROS, reactive oxygen species.

Table 3 **Anticancer properties of resveratrol in vivo.**

Reference	Model	Dose	Outcome/mechanism
Su et al. (2007)[32]	Female SCID mice with orthotropic inoculation of MCF-7 and MDA-MB-231 breast cancer cells into the mammary fat pad	10 mg resveratrol/kg BW for 2 days orally	Reduced growth of 17β-estradiol-induced MCF-7 and MDA-MB-231 human breast adenocarcinoma in mice; induced Akt inactivation and modulation of Forkhead transcription factors resulting in tumor suppression in MDA-MB-231 cells
Busquets et al. (2007)[40]	C57B1/6 mice intramuscularly inoculated with Lewis lung carcinoma	Daily i.p. dose of 5 or 25 mg resveratrol/kg BW for 15 days	No observed inhibition of primary tumor growth in mice but reduction of number of metastases by up to 40%, possibly via decreasing angiogenesis; anti-tumor activity of resveratrol may be dependent on the animal and cancer cell models used
van Ginkel et al. (2007)[30]	Mouse xenograft models of human neuroblastoma (NGP and SK-N-AS) cells	2–50 mg/kg resveratrol in Neobee M5 oil; administered orally daily for 5 weeks	Dose-dependent inhibition (up to 70–80%) of tumor growth in the mouse models despite low bioavailability in serum and tumor tissue

Abbreviations: Akt, protein kinase B; BW, body weight; i.p., intraperitoneal.

5×10^5 Lewis lung carcinoma cells, showed that resveratrol at 5 and 25 mg per kg BW per day for 15 days did not inhibit the growth of the tumor in vivo but did prevent metastasis. This result reveals the specificity of this molecule in exhibiting its activity via different pathways in the different cancer cells. Bhardwaj et al.[34] studied the effect of resveratrol in human multiple myeloma cancer cell lines. The cell lines used were human cell lines U266 (ATCC TIB-196) and RPMI 8226 (ATCC CCL-155); both cell lines are plasmacytomas of B-cell origin. The results showed resveratrol inhibits the proliferation of human multiple myeloma at a dosage of 50 μM and also prospects as an adjuvant in potentiating the apoptosis-dependent anticancer activity of thalidomide and bortezomib at 25 μM.
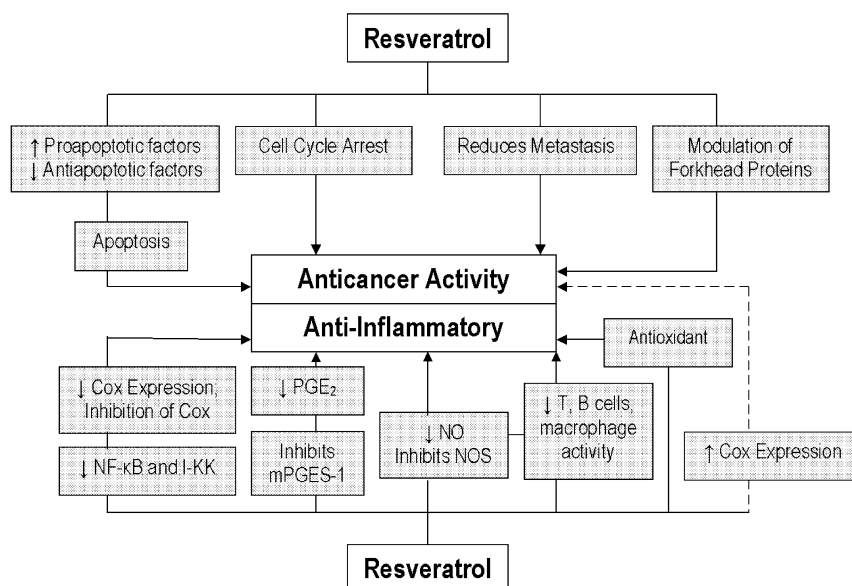
MECHANISMS OF ACTION OF RESVERATROL AGAINST CANCER

Resveratrol has shown strong anticancer properties mediated by several modes of actions (Figure 3). The most published anticancer mechanism of action of resveratrol is its ability to induce apoptosis in cancer cells via multiple pathways related to regulation of cell death and survival.[28,31,34,36,40] For example, in human neuroblastoma, resveratrol induced loss of mitochondrial membrane potential leading to the release of cytochrome C and Smac/Diablo, and subsequent activation of caspase-9 (CASP9) and caspase-3 (CASP3).[30] Caspases are cysteine proteases, and CASP9 and CASP3 are precursors of the caspase-dependent proapoptotic cascade. Trincheri et al.[31] supported this mechanism but also added that in

human colorectal cancer, resveratrol inhibited apoptosis and lysosomal cathepsin D and its post-transcriptional downregulation. Benitez et al.[39] also reported that, in addition to these mechanisms, resveratrol induced cell cycle arrest at G_0/G_1 phase and reduced the expression of cell growth factors in human prostate cancer cell lines.

Activation of other apoptotic pathways was also proposed as a possible anticancer mechanism of action of resveratrol and included increases in levels of proapoptotic Bax, p53, and p21waf in T-cell acute lymphoblastic leukemia cells;[37] decreases in levels of antiapoptotic Bcl-xL, Bcl-2, cyclin D1, and TNF receptor-associated factor 2;[34,39] and upstream inhibition of anti-apoptotic phosphatidylinositol 3′-kinase (PI3K)/Akt pathway.[38] Inhibition of the serine/threonine protein kinase Akt, also known as protein kinase B, by resveratrol has been implicated in anticancer activity mediated by activation of Forkhead proteins (FOXO3a) in human breast cancer cells in vitro and in vivo, since FOXO3a is inactivated by Akt.[32] Forkhead proteins are transcription factors that mediate cellular apoptosis through the activation of proapoptotic genes.[32] In addition to their role in programmed cell death, Forkhead proteins are involved in the regulation of several functions of the cell, including cell differentiation, DNA repair, cell cycle arrest, atrophy, and angiogenesis.[42] Thus, activation of Forkhead proteins could constitute a mechanism of the anticancer activity observed for resveratrol in human cancer cells. In addition, resveratrol had earlier been proposed to downregulate the expression of tumorigenic nuclear factor (NF)-κB and its regulated proapoptotic gene products and growth factors in multiple myeloma cells.[36] Recently, Hwang

Figure 3 Schematic representation of mechanisms of anticancer and anti-inflammatory properties of resveratrol. *Abbreviations*: COX, cyclooxygenase; IKK, I-κB kinase; I-κB, inhibitor of NF-κB; mPGES-1, microsomal prostraglandin E$_2$ synthase-1; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; PGE$_2$, protaglandin E$_2$.

et al.[37] reported that resveratrol induced apoptosis in etoposide-resistant cancer cells by activation of adenosine 5′-monophosphate (AMP)-activated protein kinase with a corresponding production of reactive oxygen species (ROS). ROS mediate the release of cytochrome C from mitochondria, which in turn leads to caspase activation and apoptosis.

In androgen-insensitive prostate cancer cells, resveratrol also activated the production of ROS, downregulated expression of anti-apoptotic factors, and upregulated the expression of pro-apoptotic factors including TNF-related apoptosis-inducing ligand (TRAIL).[43] When administered in the diet of a mouse model with prostate cancer, resveratrol significantly reduced cell proliferation with an associated decrease in growth factors and their receptors, and an increase in tumor suppressor estrogen receptor-β (ER-β) in the prostate cancer cells.[41] However, it was earlier reported that the phytoestrogenic properties of resveratrol could induce growth of estrogen-dependent human breast cancer cells based on the observation that resveratrol plays both agonist and antagonist roles in binding estrogen receptors.[44] This controversy may limit the application of resveratrol in chemoprevention. Nevertheless, resveratrol has been reported as a prospective agent in the treatment of breast cancer based on results from in vivo experiments[45] and epidemiological studies.[46]

ANTI-INFLAMMATORY ACTIVITIES OF RESVERATROL

In addition to its anticancer activity, resveratrol has displayed beneficial activity against inflammatory responses both in vitro and in vivo (Tables 4 and 5). Growing research interest into the anti-inflammatory effects of resveratrol could clinically hold a better position as an alternative to synthetic anti-inflammatory drugs. This activity is mainly based on its effect on pro-inflammatory proteins in modulating their signal transduction pathways, and on other pathways that produce precursors of inflammation.[6] Due to its activity in inhibition of pro-inflammatory gene expression in human articulate chondrocytes, resveratrol has been proposed as an anti-arthritic agent.[47] Das and Das[6] published a detailed review on the anti-inflammatory activity of resveratrol and some of its proposed mechanisms of action, mostly in inhibition of cyclooxygenase (COX) activity, inhibition of some activated immune cells, and pro-inflammatory mediators, and inhibition of transcriptional factor like NF-κB and activator protein.

MECHANISMS OF ACTION OF RESVERATROL AGAINST INFLAMMATION

Resveratrol exhibits its anti-inflammatory activity via different pathways that are mostly centered on COX-1 and COX-2. COX is the enzyme of the rate-limiting step of the pathway that produces mediators of inflammation. In addition to inhibition of COX-1 and COX-2 expression, through upstream suppression of the activity of NF-κB and I-κB kinase,[52] resveratrol reduced the production of prostaglandin E$_2$ (PGE$_2$) and the formation of ROS in lipopolysaccharide (LPS)-activated microglial cells.[48,49] Candelario-Jalil et al.[48] reported that this activity of resveratrol is based on the inhibition of the expression of

Table 4 **Anti-inflammatory properties of resveratrol in vitro.**

Reference	Model	Dose	Outcome/mechanism
El Mobrouk et al. (2006)[47]	Normal human knee articulate chondrocytes	100 μM resveratrol	Inhibition of interleukin-1 induction of pro-inflammatory (aggrecanase or ADAMT-4) gene expression in chondrocytes; prospect as an antiarthritic agent
Candelario-Jalil et al. (2007)[48]	LPS-activated primary microglial cells obtained from cerebral cortices of neonatal Sprague-Dawley rats	1–50 μM resveratrol	Dose-dependent (1–10 μM resveratrol) inhibition of LPS-induced PGE_2 production; inhibited COX-1 and total COX activities; inhibited LPS-induced microsomal PGE_2 synthase-1 gene but not COX-2 gene expressions; reduced free radical production
Kim et al. (2007)[49]	LPS-activated rat C6 microglial cells		decreased PGE_2 and NO production; inhibited LPS-induced expressions of COX-2 and nitric oxide synthase
Sharma et al. (2007)[50]	Splenocytes obtained from female BALB/c mice	1–20 μM resveratrol	Suppressed the proliferation of T- and B-cells, and macrophages; downregulated the expressions of CD28 and CD80 in a dose-dependent pattern; augmented the production of anti-inflammatory cytokine, interleukin-10
Singh et al. (2007)[51]	Purified T cells derived from C57BL/6 mice; activated with ConA	5–100 μM resveratrol	Induced apoptosis in activated T-cells

Abbreviations: COX, cyclooxygenase; LPS, lipopolysaccharide; PGE_2, protaglandin E_2.

microsomal PGE_2 synthase-1 (mPGES-1) and not COX-2 in rat microglia. mPGES-1 is directly involved in the synthesis of proinflammatory PGE_2. However, a similar study reported that the expression of COX-2 and nitric oxide synthase were inhibited by resveratrol in LPS-activated microglia.[49]

Moreover, resveratrol was reported to suppress the activity of T- and B-cells, and macrophages by decreasing the production of these proinflammatory proteins,[50] and also suppressed inflammatory processes in rat renal injury.[53] A novel pathway was also proposed for the activity of resveratrol against inflammation. Singh et al.[51] reported that resveratrol could also induce both caspase-dependent and caspase-independent apoptosis in activated T-cells in experimental allergic-encephalomyelitis-induced mice. The results show the

Table 5 **Anti-inflammatory properties of resveratrol in vivo.**

Reference	Model	Dose	Outcome/mechanism
Kundu et al. (2006)[52]	Female ICR mice with TPA induction of inflammatory activity (COX-2 expression) on the skin	0.25 or 1 μM resveratrol dissolved in 200 μl acetone applied topically to shaved mouse skin, followed by TPA treatment	Induced degradation of IκBα leading to inhibition of TPA-induced activation of NF-κB in mouse skin; reduced (at 1 μmol) TPA-induced COX-2 expressions in mouse skin by modulating the IKK/NF-κB pathway
Singh et al. (2007)[51]	C57B1/6 mice induced with experimental allergic encephalomyelitis (EAE) using myelin oligodendrocyte glycoprotein (MOG)	Daily oral dose of 100 mg resveratrol/kg BW for 30 days	Suppressed EAE in mice; Induced apoptosis in inflammatory cells in spinal cord of mice; downregulated the expression of certain cytokines and chemokines; potential in treatment of human multiple sclerosis
de Jesus Soares et al. (2007)[53]	Male Wistar rats with nephrotoxicity induced using 50% glycerol intramuscularly-injected into the hind legs	25 mg resveratrol/kg BW/day orally for 4 days starting 24 h before the glycerol treatment	Suppressed inflammatory processes in glycerol-induced rat models of nephrotoxicity leading to protection against renal injury

prospective application of resveratrol as an anti-inflammatory phytochemical. In contrast, Tang et al.[35] reported that resveratrol induced nuclear accumulation of COX-2 in human breast cancer cells, and this was associated with its p53-dependent proapoptotic activity. These results are not clear in explaining the anti-inflammatory properties of resveratrol, and further studies are needed in elucidating these contradictory observations.

SAFETY ASPECTS OF RESVERATROL TREATMENT

The literature concerning resveratrol offers a clearer explanation of the multiple bases by which this molecule operates. Moreover, Planas et al.[54] reported no hematologic or histopathologic toxicity associated with daily oral administration of resveratrol at a high dose of 20 mg/kg in rats. This dosage represents a 1000-fold higher resveratrol dosage than typically consumed by humans at the rate of one glass of red wine a day. The results of Crowell et al.[55] further support the above finding where they have shown no adverse effects in rats when administered resveratrol at 300 mg/day for 4 weeks. These evidences signify that this phytochemical could be applied as a chemopreventive agent without any adverse effects. Absence of toxicity has also been demonstrated in humans that received a single dosage of up to 5 g resveratrol.[27]

BENEFICIAL EFFECTS OF RESVERATROL IN HUMAN CLINICAL TRIALS

It is obvious that resveratrol exhibits excellent anticancer and anti-inflammatory properties, but a majority of these studies were conducted in vitro and in animal models. There is a need to investigate these physiological effects of resveratrol in humans, as the activity observed in animal models cannot be easily extrapolated to humans due to differences in metabolism and genetics. Whilst a number of human clinical trials have been conducted on the application of resveratrol in cardiovascular health, limited clinical evidence is available in the literature regarding its anticancer and anti-inflammatory properties in humans. This is due to the novelty of the therapeutic prospects of resveratrol in the treatment of cancer and inflammation, and a number of these clinical studies are underway.

One such study is a recently completed phase I clinical trial that investigated the pharmacokinetics of resveratrol.[27] This study, supported by the US National Cancer Institute and the UK Medical Research Council, evaluated the safety and plasma levels of resveratrol in healthy individuals when orally administered single doses of 0.5, 1, 2.5, and 5 g. Results of this investigation showed that a single oral dose of up to 5 g resveratrol failed to produce any significant side effects in 40 healthy volunteers of ages 19–61 years.[27] They also observed that resveratrol was present in the urine and plasma of subjects after absorption, but in a concentration significantly lower than the tentatively determined cancer chemopreventive efficacy level of at least 5 μmol/L.[27] This concentration of resveratrol could represent its minimum level capable of eliciting chemoprevention-related pharmacological effects based on data derived from various in vitro studies. The observed low plasma and urine concentrations of resveratrol was due to rapid bioconversion of resveratrol into its metabolites, which were found in high concentrations in the urine of the subjects.[27] It was based on this phenomenon that Boocock et al.[27]suggested that the monoglucoronide and sulphate metabolites of resveratrol, with plasma concentrations of 0.9–4.3 and 4–14 μmol/L, respectively, should be investigated as the possible sources of the chemopreventive activity observed for the parent molecule, in support of previous similar recommendations.[15,23] Investigation of whether target tissues are capable of converting these resveratrol metabolites into the putatively active parent molecule would be useful. Overall, the rapid metabolism of resveratrol should be seriously considered in the interpretation of the in vivo results obtained in rat models.

ONGOING CLINICAL STUDIES WITH RESVERATROL

Further search results from the US National Institute of Health Clinical Trials website show that four other clinical trials are in progress to demonstrate the cancer therapeutic effects of resveratrol in cancer patients. One of the studies is a phase I trial (NCT00433576) conducted at the University of Michigan, investigating the bioavailability and toxicity profile of resveratrol, and its effects in the expression of COX-2 and in M/G cell cycle arrest in individuals with colorectal cancer.[56] Researchers at the University of California, Irvine Medical Center are also conducting phases I and II clinical trials in patients with colon cancer (NCT00256334) to investigate the effects of resveratrol in modulating the Wnt-signalling pathway, a pathway that is implicated in the etiology of colon cancer.[57] They also propose starting another clinical intervention study using dietary resveratrol in colon cancer prevention (NCT00578396). This study will investigate if a grape juice-supplemented diet will reduce the risk of colon cancer in healthy volunteers who are 18 years of age and older.[58]

In addition to these studies, resveratrol is part of a multicomponent dietary intervention phase II clinical trial in progress at the University of Oslo (NCT00455416). This study proposes to use dietary components, including resveratrol in the form of grape juice, in the induction of

apoptosis, inhibition of cell proliferation, and modulation of tumor cell infiltrate in patients with follicular lymphoma.[59] It is expected that these studies will address the issue of extrapolation from the results of resveratrol in animal studies to therapeutic potential for humans and also provide a basis for the prospective application of resveratrol in cancer chemoprevention.

CONCLUSION

Active research is presently in progress and numerous articles have been published elucidating the mechanisms of action and the potentials of resveratrol in chemoprevention. From the perspective of nutrition, the question still remains as to how much red wine or peanuts should be taken in a day to protect an individual from developing cancers or inflammatory disease. A search for an answer to this question would consider increasing the bioavailability of resveratrol, since it is rapidly metabolized to meager levels before it gets to target tissues. Moreover, in support of previous recommendations, the major metabolites of resveratrol could be investigated for anticancer activity since they are present in significant amounts in body fluids and tissues. Should red wine emerge someday as a potent dietary source of chemopreventive resveratrol, what would the case be for high-risk young individuals who have not attained the legal age of wine consumption? Based on this scenario, further research should consider investigating the potentials of other food sources of resveratrol, like peanuts and grapes, in anticancer and anti-inflammation chemoprevention. And what about the other potentially bioactive polyphenols present in red wine? This suggests that further research should also be carried out to investigate the chemopreventive effects of commercial red wines in humans. Taking all the research investigations conducted so far into consideration, there is no doubt that resveratrol, or the commercial products in which it is present, including red wine, would eventually emerge as therapeutic agents in the management and treatment of cancer and inflammatory diseases.

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