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Review article

# Resveratrol: An overview of its anti-cancer mechanisms

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ABSTRACT

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

## 1. Introduction

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

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

## 2. Pharmacokinetics of resveratrol

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

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

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

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

## 3. Resveratrol inhibits cancer

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

### 3.1. Colorectal cancer

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

#### 3.1.1. Resveratrol protects against CRC

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

#### 3.1.2. Resveratrol as a therapy for CRC

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

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

### 3.2. Skin carcinogenesis

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

#### 3.2.1. Resveratrol protects from the development of skin cancer

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

#### 3.2.2. Resveratrol as a therapy for skin cancer

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

## 4. Anti-cancer mechanisms of resveratrol

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