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Anti-Cancer Effects of Resveratrol – In Vivo Evidence

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ABSTRACT:

An increasing number of people worldwide are impacted by cancer each year. Thanks to the efforts of physicians and scientists, the overall survival rates of the majority of tumors have increased. But some tumors become resistant to chemo radiotherapeutic drugs, therefore researchers studying cancer are still looking for efficient sensitizers. Improved metabolism, cardioprotection, and cancer prevention are just a few of the anti-aging health advantages of resveratrol, a naturally occurring polyphenol. The majority of research on resveratrol and cancer is based on in vitro investigations that examine the effects of resveratrol on cancer pathways and cells. However, the number of research examining the in vivo effects of resveratrol treatment on cancer outcomes is rather few; this may be due to the compound's low oral bioavailability. Although resveratrol has been demonstrated to have favorable and prospective effects in cell culture research, there is conflicting evidence from rodent and human studies. The in vivo effects of resveratrol treatment on pancreatic, liver, colorectal, breast, and prostate cancers are highlighted in this article. A naturally occurring phytoalexin, resveratrol (3,5,40-trihydroxystilbene) is found in a variety of fruits and vegetables, including red wines, black olives, capers, almonds, grapes, and apples.

Introduction

As the second greatest cause of mortality in America, cancer is a serious global public health issue. More than 600,000 people will die from cancer-related causes and more than 1.6 million new cases of the disease are expected in 2017, according to the American National Center for Health Statistics. [(1)] The most popular cancer treatments include radiation, chemotherapy, and surgery. Since many cancer patients are identified at advanced stages after the window for surgery has passed, chemotherapy and radiation therapy are employed as the main treatment regimens for the majority of cancer patients and play crucial roles in cancer treatment. But a significant obstacle in cancer treatment is that an increasing number of cancers are developing resistance to radiotherapy and chemotherapy (known as radio resistance and chemoresistance, respectively). Moreover, problems arise when cancer cells acquire resistance to chemotherapeutic drugs and radiation therapy through various mechanisms, and these treatments frequently result in unfavorable outcomes. Consequently, we must find a novel approach or treatment substance that can get past radioresistance and chemoresistance. A growing number of natural compounds have been found to be efficient anticancer medications in recent years, thanks to benefits like multitargeting capabilities, instant availability, affordability, and minimal toxicity. Commonly present in fruits and vegetables, polyphenols have been shown to have a variety of therapeutic benefits on cancer and other chronic illnesses. A traditional natural polyphenolic phytoalexin, resveratrol (trans-3,4,5-

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trihydroxystilbene) is present in many plants and traditional Chinese medicines (e.g., white hellebore, grape skin, red wine, Rheum officinale Baill, berries, peanuts, and Polygonum cuspidatum). [2] Numerous investigations have confirmed resveratrol's anti-inflammatory, antioxidant, and heart-healthy preventive properties. Nevertheless, more research is necessary to fully understand the precise molecular pathways by which resveratrol treats cancer. [3] Because resveratrol can induce growth inhibition, cell cycle arrest, and apoptosis in several human cancer cell lines, it has been shown in numerous studies over the past few years to directly inhibit the proliferation and viability of cancer cells in vitro in a dose- and time-dependent manner. Additionally, resveratrol has been shown in numerous reports to have the potential to be used as a cancer chemopreventive agent. While resveratrol has demonstrated numerous anticancer benefits, the exact mechanisms by which these effects are mediated remain unclear. [4] This paper aims to examine the latest developments in the utilization of resveratrol and its derivatives in cancer therapy. Particular attention will be given to the function of resveratrol in the tumor microenvironment and in cancer cell sensitization to chemotherapy and radiation, as well as its associated mechanisms and potential uses in the future. [5] A "miracle" nutraceutical called resveratrol (3,4',5-trihydroxy-trans-stilbene) holds the potential to treat cancer and signal advancements in cancer treatment. Plants naturally manufacture resveratrol, a phytoalexin, to guard against disease invasion and environmental stress. It was first isolated in 1940 from the roots of the white hellebore plant, Veratrum album, and then removed in 1963 from the roots of the Japanese knotweed species, Polygonum cuspidatum. [6,7,8,] Despite the fact that its cardioprotective properties were first reported in 1982, the molecule gained popularity only after it was proposed in 1992 that the resveratrol found in red wine provided cardioprotective health advantages. Topical resveratrol's potential application as a novel anticancer medication was brought to light in 1997 when it was discovered to inhibit carcinogenesis in a mouse model of skin cancer. More than seventy plants contain resveratrol that can be extracted.[9,10,11,12] Natural foods like peanuts and pistachios contain it, and bilberries and blueberries also contain it in smaller levels. [13,14] It is frequently found in wine and extracted from grapes, whose skins have a high concentration of resveratrol. Resveratrol can also be found in chocolate, raw cranberry juice, and items that contain cocoa powder. There are two geometric isomers of resveratrol. [15,16,17] Because of its instability, its cis-isomer is not accessible for purchase. Although its trans-isomer is more stable, heat speeds up the process of breakdown, which causes it to change into the cis-isomer when exposed to high pH or UV light. [18,19] The anticancer and health effects of resveratrol are thought to be attributed to the trans-isomer, aside from its higher stability and biological activity when compared to the cis-isomer. As a result, the study has concentrated on using its trans-isomer therapeutically. [20,21] From increasing immunity to delaying the aging process and imitating the effects of calorie restriction, resveratrol offers an endless array of health benefits. It also has specific actions that prevent or lessen diseases like diabetes, as well as neurodegenerative and cardiovascular diseases. [22,23] Most notably, a great deal of study has confirmed its ability to suppress cancer. In addition to its effectiveness as a chemopreventive agent in the four main stages of carcinogenesis—initiation, promotion, advancement, and metastasis—resveratrol has also been demonstrated in vitro and in vivo for the treatment of cancer. [24] Given its anti-inflammatory, direct anti-tumor, and antioxidant characteristics, resveratrol is a highly promising adjunct to traditional chemotherapy. It has demonstrated effectiveness against lung, skin, and hematological malignancies as well as obesity-related cancers such hepatic, pancreatic, postmenopausal breast, prostate, and colorectal cancer. [25] Numerous reviews have provided an overview of the different channels and mechanisms through which resveratrol works. [26-32]

Resveratrol regulates the level of reactive oxygen species

Proteins, lipids, and nucleic acids can be harmed by reactive oxygen species (ROS), which include hydrogen peroxide (H2O2), hypochlorous acid (HOCl), and free radicals such as hydroxyl radical (• OH), superoxide anion (• O2–), and lipid peroxides. The majority of malignant tumor cells have been shown to have elevated ROS levels, which are crucial for the development and spread of cancer by encouraging cell division, survival, invasion, and metastasis. Resveratrol's anticancer effects are probably partly due to its ability to modulate antioxidant enzyme activity. Resveratrol has the ability to mechanistically increase the production of enzymes such as glutathione peroxidase, catalase, and superoxide dismutase (SOD) as well as their enzymatic activity in tumor cells. This ultimately causes an accumulation of H2O2 in the mitochondria and induces apoptosis in cancer cells. Conversely, the protective action of resveratrol on normal cells may be explained by a minor overexpression of antioxidative enzymes and a reduction in oxidative stress. According to research by Jung et al., resveratrol can reduce intracellular ROS levels and decrease the accumulation of hypoxia-inducible factor-1 (HIF-1), which in turn inhibits the uptake of 18F-FDG by lung, colon, and breast cancer cells as

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well as glycolytic metabolism. According to Kong et al., pterostilbene, a naturally occurring dimethylated derivative of resveratrol, can cause human diffuse large B cell lymphoma cells to undergo apoptosis both in vivo and in vitro by suppressing ERK1/2 and activating the p38 mitogen-activated protein kinase (MAPK) signaling pathways. This could help to explain why resveratrol and other chemotherapeutic medications combined have more potent anticancer effects. Vendrely et al. found that treatment with capsaicin and resveratrol analogues increased the formation of ROS in pancreatic adenocarcinoma. This led to the activation of the p38 MAPK pathway and upset the balance of Bcl-2 and BAX expression, ultimately causing apoptosis. Additionally, Kim et al. discovered that either separately or in combination, capsaicin and resveratrol inhibited cell growth and induced cell apoptosis by upregulating NO production and Bax expression, which was accompanied by a decrease in MDM2, Bcl-2, and cytochrome c expression as well as the activation of caspase-9, caspase-3, caspase-8, death receptor 4, and Fas (CD95). These findings suggest that capsaicin and resveratrol collectively induce cell apoptosis by activating the mitochondrial and death receptor pathways. [33,34,35,36,37]

Pre-clinical studies

Significant anti-cancer properties of resveratrol have also been demonstrated in a number of preclinical animal models. (Table 1) [38]

Skin Cancer

A two-stage mouse skin carcinogenesis model, begun by 7,12-Dimethylbenz[a]anthracene (DMBA) and accelerated by 12-O-tetradecanoyl-13-acetate (TPA), was used to present the first preclinical research of resveratrol's anti-cancer or chemopreventive action. After then, xenograft models, ultraviolet B radiation (UVB) exposure, DMBA/TPA, DMBA alone, TPA alone, and benzo[a]pyrene (BP) have all been used in a number of in vivo skin cancer investigations. Resveratrol therapy lowered the incidence, multiplicity, and tumor volume in the DMBA/TPA mice while delaying the start of carcinogenesis. Resveratrol proved efficacious at all phases of carcinogenesis and stopped mice's DMBA/TPA-induced skin cancer from growing.

Through the stimulation of apoptosis, as evidenced by the induction of cytochrome c release, the expression of Bax, p53, and Apaf-1, and the suppression of Bcl-2, resveratrol substantially prevented the growth of DMBA/TPA-induced mouse-skin tumors. Resveratrol was found by Afaq et al. to be able to decrease edema and inflammation in the skin of SKH-1 hairless mice after short-term UVB exposure; this effect may be attributed to the suppression of ornithine decarboxylase. Resveratrol therapy inhibited the growth of skin tumors both before and after UVB exposure. The anti-tumor effects of resveratrol have also been connected to increased levels of E-cadherin expression and decreased levels of TGF-β1 expression. The development of a mouse melanoma xenograft (B16BL6 cell line) carried in mice was inhibited by oral gavage of resveratrol, resulting in lower expression of Akt. In a mouse model of human cutaneous skin squamous carcinoma A431 cell-line xenograft, resveratrol therapy decreased survivin expression, increased p53 and ERK expression, and decreased tumor volume. Nevertheless, resveratrol did not stop the formation of tumors in mice that were xenografted with A375, B16M, or DM738 melanoma cell lines. [38]

Breast Cancer

Resveratrol has been shown to have anti-cancer and chemopreventive properties in a number of animal models of breast cancer. In models of spontaneous mammary tumors with HER-2/neu-overexpressed or Brca1-mutant (K14cre; Brca1F/F; p53F/F) mice, as well as models of chemically induced mammary-gland carcinogenesis using N-methylnitrosourea (MNU), estradiol, or DMBA, the preventive or curative effects of resveratrol have been studied. Additionally, it has been found that oral resveratrol reduces the amount of cancer that rats develop from N-nitoso-N-methylurea (NMU). In a xenograft animal model, resveratrol suppressed the growth of ER-α–negative tumor explants and ER-β–positive MDA-MB-231, but enhanced apoptosis and reduced angiogenesis in nude mice. However, resveratrol had no influence on the in vivo proliferation and metastasis of transplanted ER-α–negative 4T1 murine breast cancer cells in nude mice. Bove et al. used intraperitoneal dosages of 1-4 mg/kg per day to study the effects of resveratrol in vivo. They proposed that the reason for this inefficiency could have been a low resveratrol dosage. In a different study, oral resveratrol at 100 or 200 mg/kg stopped mice's 4T1 cells from growing and from developing lung metastases. The observed outcomes were linked to a reduction in MMP-9 expression and activity. These results suggest that resveratrol's effectiveness to prevent breast cancer depends on its dosage and manner of administration. [38]

Prostate Cancer

Prostatic cancer incidence was significantly reduced in the transgenic adenocarcinoma mouse prostate (TRAMP) model

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by dietary resveratrol. In the TRAMP model of prostate cancer, resveratrol inhibited the progression of the disease by downregulating the expression of the androgen receptor (AR). Resveratrol also lowered the mRNA level of androgen-responsive glandular kallikrein 11, which has been identified as an ortholog of the human prostate specific antigen (PSA), in addition to downregulating the expression of AR. Resveratrol slowed the growth of AR-positive LNCaP tumors and suppressed the expression of markers related to the steroid hormone response in a xenograft model. Using AR-negative PC-3 human prostate cancer-cell xenografts in the flank areas of mice, oral resveratrol (30 mg/kg/day) was administered as a post-treatment to reduce tumor volume, induce apoptosis, and reduce tumor-cell proliferation and neovascularization. The tumor volume of PC-3 cell xenografts in mice prostates was likewise reduced by intraperitoneal post-treatment with resveratrol (25 mg/kg/day). Furthermore, in the orthotopic DU-145 prostate cancer model, intraperitoneal post-treatment of resveratrol (50 mg/kg/day) lowered tumor growth, progression, local invasion, and spontaneous metastasis. [38]

Colorectal Cancer

Numerous variables, including a diet high in red and processed meat as well as lifestyle choices like drinking alcohol and smoking, can contribute to colorectal cancer. The efficacy of resveratrol in vivo has been investigated using genetically engineered ApcPirc/+ rats and ApcMin/+ mice as colon cancer models. Azoxymethane (AOM), AOM + dextran sulfate sodium (DSS), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, 2-amino-3-methylimidazo[4,5-f]quinoline, and 1,2-dimethylhydrazine (DMH) are among the chemical carcinogens that can cause colon cancer. The pathophysiological and histological characteristics/manifestations associated with colon cancer are hyperplasia, adenocarcinoma, adenoma, and aberrant crypt foci (ACF). Oral resveratrol therapy (by gavage or diet) reduced the incidence, individual size, and multiplicity of ACF in mouse models induced with AOM or AOM plus DSS, and altered biomarkers. Resveratrol decreased the expression of COX-2, inducible nitric oxide synthase (iNOS), TNF-α, aldose reductase, NF-κB [261], and p-protein kinase C-β2 (PKC-β2). It increased the expression of Bax, p53, and p-p53 at Ser15, HO-1, glutathione reductase (GR), and Nrf2. Resveratrol has been suggested to downregulate the activation of NF-κB and PKC-β2 that is dependent on aldose reductase, which results in a decrease in the expression levels of COX-2 and iNOS. Resveratrol reduced histopathological lesions, DNA damage in leukocytes, and the frequency, size, and multiplicity of ACF in animals produced with DMH. Resveratrol's anti-tumor effects against colon carcinogenesis were shown to be accompanied by changes in enzyme activity. Antioxidant enzyme processes, such as those of catalase (CAT) and SOD in the intestine/colon, liver, and erythrocytes, were increased in rat models, while biotransforming enzyme processes, such as those of β-glucosidase, β-glucuronidase, β-galactosidase, nitroreductase, and mucinase, were decreased in fresh fecal and colonic mucosal samples. Resveratrol increased the expression levels of caspase-3 in the colonic mucosa and decreased the levels of ODC, COX-2, Mucin 1, cell surface associated (MUC1), heat-shock protein (Hsp)27, and Hsp70. It also increased the levels of glutathione in the reduced state (GSH) in the liver, intestine/colon, plasma, and erythrocytes. [38]

Pancreatic cancer

Consumption of animal products, high-fat diets, and obesity are associated with an increased risk of pancreatic cancer. Patients with pancreatic cancer typically have a poor prognosis since a large number of these cases are detected at late, treatment-refractory stages. It is obvious that effective pancreatic cancer therapy options are needed. A small number of researchers have examined resveratrol's effects on pancreatic cancer in vivo. In order to encourage the establishment of pancreatic tumor xenografts, Oi et al. (2010) injected human pancreatic cancer cells (PaCa-2) into 6-to 8-week-old Swiss nude mice. Prior to the MIA PaCa-2 injection, resveratrol was administered orally five times a week at a dose of 10 or 50 mg/kg BW. This dosage was maintained for the duration of the experiment until the tumor volumes reached 1 cm3. When compared to mice given a vehicle control dose, resveratrol decreased tumor size and number in a dose-dependent way. Leukotriene A4 hydrolase, an inflammatory enzyme, was likewise suppressed by resveratrol. In a related study, Harikumar et al. (2010) injected male 4-week-old mice with MIA PaCa-2 cells, and starting one week following the injection, the animals were administered 40 mg/kg BW of resveratrol daily for four weeks. When compared to mice given a vehicle treatment, they discovered that resveratrol administration dramatically slowed the formation of tumors. Resveratrol and gemcitabine combined therapy improved protection much more. When resveratrol (20, 40, or 60 mg/kg BW by gavage) was administered five times a week to 4- to 6-week-old BALB/c nude mice beginning one week after the tumor cell injection, the amount of tumor growth induced by the injection of PANC-1 cells (human pancreatic carcinoma, epithelial-like

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cells) was decreased in a dose-dependent manner in comparison to control mice (Roy et al. 2011). When compared to tumor tissue from mice treated with a vehicle, the tumor tissues from mice treated with resveratrol exhibited higher apoptosis and lower proliferation. The transcription factor Forkhead box O (FOXO) was activated more when PI3K and Akt phosphorylation were inhibited concurrently with this. The expression of genes implicated in cell-cycle arrest is triggered by FOXO activation, suggesting that resveratrol inhibited tumor growth by influencing the cell cycle (Roy et al. 2011). Resveratrol treatment for ten months, administered five times a week (40 mg/kg BW by oral gavage), decreased pancreatic lesions in eight-week-old KrasG12D mice that spontaneously develop pancreatic tumors. This suggests that resveratrol inhibits the growth of spontaneous pancreatic tumors in comparison to KrasG12D mice that do not receive resveratrol treatment (Shankar et al. 2011). However, no animal model of pancreatic cancer has been used to demonstrate the benefits of resveratrol administration. Kuroiwa et al. (2006) conducted a study on 6-week-old male Syrian hamsters and examined the effects of resveratrol administration (0.001% in diet) both during and after tumor initiation via N-nitrosobis(2-oxopropyl)amine injection. During either treatment phase, resveratrol had no effect on the development of hyperplasias or adenocarcinomas. In any case, available data indicate that resveratrol either has a beneficial effect on pancreatic cancer outcomes in mouse models or has no discernible effect. [39]

Liver Cancer

A lower incidence and fewer nodules in animal models using chemical carcinogens (e.g., diethylnitrosamine (DENA), DENA plus phenobarbital, and DENA plus 2-acetylaminofluorene (2-AAF) or transgenic mice (e.g., hepatitis B virus X protein (HBx)-expressing transgenic mice) demonstrated the anti-cancer potential of resveratrol in liver carcinogenesis. Furthermore, in xenograft models using hepatoma cell lines (e.g., H22, AH-130, HepG2, and AH109A), resveratrol's anti-tumor activities have been documented. Dietary resveratrol increased the synthesis of protein carbonyl and totally inhibited DENA-induced lipid peroxidation, suggesting that it may also lessen oxidative stress in the liver. Additionally, resveratrol decreased the level of iNOS and increased the expression of hepatic Nrf2. According to that study, Nrf2 signaling's transcriptional and translational regulation may be responsible for the reduction of oxidative and nitrosative stress as well as the attenuation of the inflammatory response. Recent investigations using Nrf2-deficient animals have demonstrated that Nrf2 contributes to liver protection against hepatocarcinogenesis triggered by xenobiotics. The potential of resveratrol to prevent or treat hepatocellular carcinoma has been investigated by Rajasekaran et al. Resveratrol is administered either at the time of DENA injection or for a period of 15 days following the onset of hepatocellular carcinoma. In addition to reducing cell crowding and alterations in cellular architecture, resveratrol administration at both time points also resulted in smaller livers in comparison to control rats given DENA. Resveratrol treatment prevented the formation of hepatocyte nodules in the DENA-induced hepatocellular cancer model by downregulating the levels of Hsp70 and COX-2 and by reducing the translocation of NF-κB from the cytoplasm to the nucleus. It was also discovered in another investigation that the hepatic TNF-α, IL-1β, and IL-6 generated by DENA can be reversed, using the same amount of resveratrol. In the course of DENA-induced hepatocellular carcinogenesis, resveratrol also shown a notable anti-angiogenic effect; this effect may have been achieved by inhibiting VEGF expression through the down-regulation of HIF-1α. Rats were given an injection of Yoshida AH-130 ascites hepatoma, a rapidly expanding tumor, and resveratrol significantly reduced the number of cells in the tumor, causing apoptosis and cell accumulation in the G2/M phase. It was also shown that the injection of resveratrol to mice transplantable liver tumors inhibited the advancement of the cell cycle by reducing the levels of p34cdc2 and cyclin B1. Additionally, resveratrol has been shown to have anti-tumor-growth and anti-metastasis properties in Donryu rats that were implanted subcutaneously with an AH109A hepatoma cell line for ascites. In a different study, using a mouse model of hepatoma xenograft, resveratrol decreased angiogenesis and tumor growth. Salado et al. investigated the effects of resveratrol administration on hepatic metastasis, which is primarily brought on by the generation of pro-inflammatory cytokines, using B16 melanoma (B16M) cells. Lin et al. looked at how resveratrol treatment affected the precancerous stage of liver carcinogenesis in HBx transgenic mice with spontaneously produced hepatocellular carcinoma. Supplementing with resveratrol enhanced the delay of tumor formation and greatly decreased the incidence of hepatocellular carcinoma. Resveratrol decreased intracellular ROS and hepatic lipogenesis. Consistently positive outcomes from liver cancer models suggest that resveratrol may be useful in the prevention and/or treatment of hepatocellular carcinoma. [38]

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Table 1. In vivo anti-cancer effects of resveratrol.

Cancer model	Animal model	Dose	Outcomes
Breast	Spontaneous mammary tumor in female FVB/N HER-2/neu mice	4 µg/mouse/day in drinking water for 2 months	Onset of tumorigenesis↓ Tumor volume↓ Multiplicity↓ Apoptosis↑
	Female athymic mice xenograft models of MDA-MB-231 cells	25 mg/kg/day i.p. daily for 3 weeks	Tumor volume↓ TUNEL staining↓ Microvessel density↓
	Female Balb/c mice xenograft with cigarette smoke condensate-transformed, MCF-10A-Tr cells in mammary fat pad	40 mg/kg/day orally for 30 days	Tumor volume↓
	DMBA-induced mammary carcinogenesis in female Sprague-Dawley rats	10 ppm mixed in diet; for 127 days	Suppressed tumor growth NF-κB↓ Cox2↓ MMP9↓
Prostate	Athymic nude mice xenograft models of PC-3 cells	30 mg/kg/day Thrice/week, total 6 weeks	Tumor volume↓ Cell proliferation↓ Apoptosis↑ Number of blood vessels↓
	Male nude mice xenograft models with Du145-EV-Luc or Du145-MTA1 shRNA-Luc in anterior prostate	50 mg/kg/day i.p. daily 14 days after implantation, total 6 weeks	Tumor growth↓ Progression, local invasion↓ Spontaneous metastasis↓ Angiogenesis↓ Apoptosis↑
	Transgenic adenocarcinoma of mouse prostate (TRAMP) model	625 mg/kg mixed in diet for 7–23 weeks	ER-β ↑ IGF-I ↑ ↓phospho-ERK-1 ↓ERK-2

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	Transgenic rat adenocarcinoma of prostate (TRAP) model	50, 100 or 200 µg/ml in drinking water for 7 weeks	Apoptosis ↑ ↓AR ↓GK11 mRNA
Skin	DMBA/TPA model in female CD-1 mice	1, 5, 10, 25 µmol topically twice/week for 18 weeks	Incidence↓ Number of tumors per mouse↓
	DMBA-initiated and TPA-promoted papillomas in female ICR mice	85 nmol/L for 21 days; topical application	Prevent onset of skin tumor
	UVB-induced skin tumorigenesis in female SKH-1 mice	25, 50 µmol/mouse; twice/week for 28 weeks; topical application	Suppresses melanoma tumor growth
Colon	DMH models in male Wistar rats	8 mg/kg/day orally daily for 30 weeks	Incidence↓ Tumor volume↓ Tumor burden/rat↓ Histopathological lesions DMH↓
	BP models in male ApcMin mice	45 µg/kg/day orally, for 60 days	Number of colon adenomas↓ Dysplasia occurrence↓
	ApcMin/+ mice model	240 mg/kg b.w. mixed in diet for 10–14 weeks	Suppress intestinal adenoma formation Cox1 and 2↓ PGE2↓
Liver	Male Donryu rats xenograft models of AH109A cells	10, 50 ppm in diet for 20 days	Tumor weight↓ Metastasis↓
		1 mg/kg; 7 days; i.p.	Tumor weight↓ Apoptosis↑

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	Male Wistar rats implanted with AH130 hepatoma cells		↑cells at G2/M
	DENA-initiated GST-P-positive hepatic pre-neoplastic foci in male Sprague–Dawley rats	15% (w/w) grape extract in diet; 11 weeks	Tumor growth↓ Lipid peroxidation↓ Fas ↓

Additional research is necessary to fully understand the clinical uses of resveratrol.

Is resveratrol safe?

Forty healthy volunteers were enrolled and split into four groups to study the safety and pharmacokinetics of resveratrol prior to its use in cancer prevention and therapy. Each group was given a dose of 0.5, 1.0, 2.5, or 5.0 g of resveratrol for four weeks (Table 2). Resveratrol was quickly absorbed, and approximately one hour after consumption, it produced its highest concentration. Resveratrol's half-life for plasma elimination ranged from 4.77 to 9.70 hours. Participants who received greater doses of resveratrol (2.5 and 5.0 g) were more likely to experience moderate gastrointestinal discomfort, such as diarrhea, nausea, flatulence, and abdominal discomfort, which accounted for the bulk of adverse events. During the study period, every participant showed normal performance status and no weight loss was detected in any of them. Resveratrol's safety was confirmed in patients with treatable colorectal cancer in order to look into it. Before surgery, patients took 0.5 or 1.0 g of resveratrol every day for 8 days. As with the earlier report, patients responded well to dosages of 0.5 or 1.0 g, and no side effects associated with resveratrol were noted. These findings imply that resveratrol use is generally safe, even though mild to severe gastrointestinal pain is a common side effect. [40,41,42]

Resveratrol demonstrated encouraging results in the prevention and treatment of cancer.

To confirm resveratrol's function in cancer prevention and therapy, 39 adult women at high risk of breast cancer were enlisted to study resveratrol's cancer-preventive properties (Table 2). Following a 12-week period of daily resveratrol or placebo ingestion, mammary ductoscopy specimens were obtained from each participant, and the methylation of p16, CCND2, RASSF-1, and APC was examined. This study showed that resveratrol consumption reduced RASSF-1 methylation, which is related to cancer, apoptosis, and cell cycle regulation. One possible method by which resveratrol suppresses carcinogenesis is through modulating enzymes involved in carcinogen activation and detoxification, as suggested by a prior clinical research. In colorectal cancer, resveratrol induced apoptosis as evidenced by an increase in the immunostaining of cleaved caspase 3.74 and decreased the immunostaining of Ki-67, which is only produced in proliferating cells and functions as a growth-promoting factor for cells. It is yet unknown, nevertheless, if resveratrol supplementation can stop cancer from spreading or increase a patient's overall survival. Resveratrol's potential as a treatment for patients with relapsed and/or refractory multiple myeloma (MM) was assessed in a phase II research. SRT501 is a micronized version of resveratrol. Patients in the phase II clinical trial of SRT501, with or without bortezomib, had relapsed MM or were refractory to at least one prior therapy. However, in patients with relapsed/refractory MM, this phase II study revealed poor effectiveness and an unacceptable safety profile of SRT501 (5.0 g). We come to the conclusion that more clinical research on resveratrol is necessary. **(43,44,45,46)**

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Table 2. Clinical trials of resveratrol in healthy volunteers or patients with malignant disease

Author	Purpose	Participants	Dose	Results
Brown et al.	To assess its safety and pharmacokinetics	40 healthy volunteers	0.5, 1.0, 2.5, or 5.0g	Resveratrol was safe, but the 2.5 and 5 g doses caused mild-to-moderate gastrointestinal symptoms
Patel et al.	To measure concentrations of resveratrol and its metabolites in colorectal tissue of humans who ingested resveratrol	20 patients with histologically confirmed colorectal cancer	0.5 or 1.0 g	Daily oral doses of resveratrol at 0.5 or 1.0 g produce levels in the human gastrointestinal tract of an order of magnitude sufficient to elicit anticarcinogenic effects
Chow et al.	To determine the effect of resveratrol on drug and carcinogen metabolizing enzymes	42 healthy volunteers	1.0 g	Resveratrol can modulate enzyme systems involved in carcinogen activation and detoxification, which may be one mechanism by which resveratrol inhibits carcinogenesis
Zhu et al.	To assess the effect of resveratrol on DNA methylation and prostaglandin expression in humans	39 adult women at increased breast cancer risk	5 or 50 mg	Resveratrol decreased the methylation of the tumor suppressor gene RASSF-1

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Conclusion

Resveratrol has been shown to be able to attenuate the several phases of carcinogenesis using a range of in vivo and in vitro models. A few of these stages are briefly listed in Figure 1. Resveratrol has demonstrated a significant deal of promise as an anti-cancer agent, both for the prevention and therapy of a wide spectrum of malignancies, through an extensive body of experimental in vivo and in vitro research as well as a few clinical trials. Resveratrol is extremely low in toxicity and, although having a variety of molecular targets, it functions on various common and protective pathways that are frequently changed in a large number of cancers. This implies that resveratrol could be a better candidate for usage as an anti-carcinogen. It can also work in concert with other chemotherapeutics and targeted therapies to efficiently exercise its antineoplastic effects. It is possible to stop carcinogenesis by inhibiting inflammation, oxidative stress, and the growth of cancer cells as well as by activating carefully controlled mechanisms that kill cancer cells. Studies have indicated that taking resveratrol supplements may offer numerous health advantages, such as a lower risk of cancer. However, the outcomes of animal models have been inconsistent, and there are few small-scale clinical trials. Studies using animal models need to be conducted more thoroughly and consistently. The most potential application of resveratrol is probably as a cancer preventive agent because there is little indication that it can be used to treat preexisting tumors (tumors that were not implanted cells). Future research investigations and clinical trials are likely to focus on determining the appropriateness and efficacy of resveratrol as an anti-cancer or cancer preventive agent. Because distinct oncogenic pathways are specific to different tumor types, and because resveratrol has a suggested method of action, it may affect some tumor types more than others. Furthermore, there is still more work to be done to optimize the drug's bioavailability and determine its pharmacokinetic, pharmacodynamic, and safety profile in various patient populations, such as adults, pregnant women, and children

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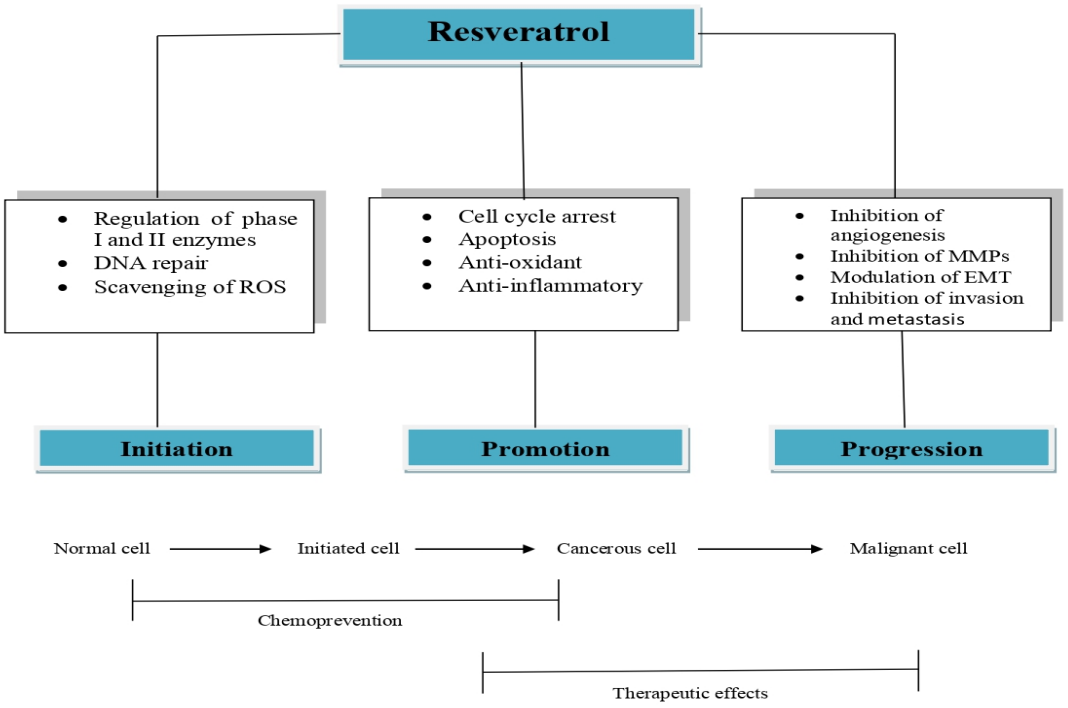

Figure 1. A schematic diagram summarizing the potential mechanism(s) underlying the anticancer effects of resveratrol.

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