REVIEW

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Resveratrol and Its Anticancer Effects

Resveratrol ve Antikanser Etkileri

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ABSTRACT

Cancer is a worldwide public health problem and is the second leading cause of death in the world. Resveratrol, which is an antioxidant molecule belonging to the polyphenol family, is usually extracted from a large number of natural plants. Recently, many studies have been conducted on resveratrol and its effect on cancer. In this review, the effects of resveratrol are emphasized on chemopreventive, therapeutic, and anticancer. More than 70 related scientific articles from various databases (e.g.; Science Direct, MDPI, PubMed, and Google Scholar) were evaluated for this review using the keywords anticancer, antioxidant, apoptosis, cancer, resveratrol, tumorigenesis. It has been revealed that resveratrol is associated with many biochemical pathways that are effective in the formation, development, and spread of cancer.

Keywords: Anticancer, antioxidant, apoptosis, cancer, resveratrol, tumorigenesis

ÖZ

Kanser dünya çapında bir halk sağlığı sorunudur ve dünyada ölüm nedenleri arasında ikinci sırada yer almaktadır. Polifenol ailesine ait antioksidan bir molekülü olan resveratrol, genellikle çok sayıda doğal bitkiden ekstrakte edilir. Son zamanlarda resveratrol ve kanser ile ilgili birçok çalışma yapılmıştır. Bu derlemede resveratrolün kemopreventif, terapötik ve antikanser etkileri üzerinde durulmuştur. Bu derleme çalışması için antikanser, antioksidan, apoptoz, kanser, resveratrol, tümörogenez anahtar kelimeleri kullanılarak çeşitli veri tabanlarından (örneğin; Science Direct, MDPI, PubMed ve Google Scholar) 70'ten fazla ilgili bilimsel makale değerlendirilmiştir. Resveratrolün kanser oluşumunda, gelişiminde ve yayılmasında etkili olan birçok biyokimyasal yolaklarla ilişkili olduğu ortaya koyulmuştur.

Anahtar Kelimeler: Antikanser, antioksidan, apoptoz, kanser, resveratrol, tümörogenez

Introduction

Resveratrol (3, 4', 5-trihydroxystilbene; RSV) is a stilbene phytoalexin which is a kind of natural phenol and is composed part of the defense system in plants (1). It was first isolated from the roots of *veratrum grandiflorum* by Takaoka in 1939. RSV is a polyphenolic compound with different mechanisms of action found in grapes, wine, peanuts, and blueberries (2). There are two geometric isomers of RSV as cis- (Z) and trans- (E) in Figure 1 (3). The trans isoform is biologically active. The trans form can be found industrially in cosmetic ingredients or used as a food supplement, which is obtained from yeast extracts recombinantly.

Additionally, its isomerizes to the cis form by exposing to ultraviolet radiation, light, or heat (4). Recent studies have been shown that RSV has many effects, such as antioxidative, antiinflammatory, cardioprotective, antidiabetic, anticancer, chemopreventive, and neuroprotective effects (5). It achieves all these effects by targeting tumor angiogenesis, apoptosis regulators, cell survival, metastasis and intracellular

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signaling factors, including key components such as proinflammatory mediators, a different set of transcription factors and many signaling pathway regulators (6).

Cancer is a disease characterized by abnormal, uncontrolled cell growth that has the potential to spread to other parts of the body (7). Its the second most common cause of death in the world after cardiovascular diseases. There are 19.3 million new cancer cases and approximately 10.0 million cancer-related deaths worldwide in 2020. In both sexes, lung cancer accounts for 11.6% of all cases and is the most frequently diagnosed cancer. Considering their incidences, female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) are followed up lung cancer, respectively (8). The treatments recently applied to cancer patients in the clinic include immunotherapy, chemotherapy, radiotherapy, and surgical operation (9). However, all these treatment strategies can damage the cancer patients and the immune system of the person (10). Nowadays, since plants and fruits are naturally rich in beneficial components for the body, new drugs are being researched for new drug formations, and it is thought that they may be a new treatment option for many diseases that cannot be cured (11). In recent years, the effects of RSV as a functional nutritional component, which has beneficial biological effects on health and cancer, have attracted attention (12).

RSV Content of Foods

Primary dietary sources of RSV are grapes, peanuts, strawberries, and legumes (13). The major source is grapes because the compound is also found in wine which is one of the grape's end products. However, its highest levels are naturally found in the roots of Japanese Knotweed (*Polygonum cuspidatum*), which is used in traditional Asian herbal medicine (14). Today, other sources can also be identified. The RSV contents of foods show the studies carried out in Table 1 (15,16).

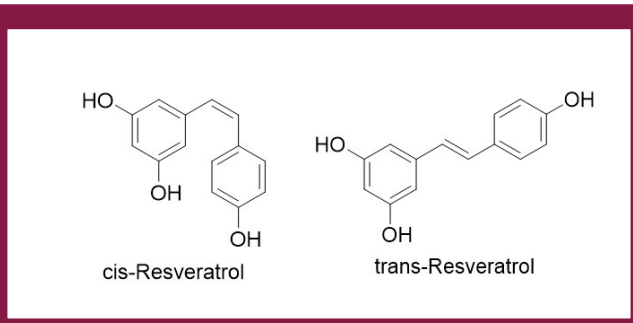


Figure 1. Cis- and trans-configuration of resveratrol

Biosynthesis and Bioavailability of RSV

There are two main pathways for RSV production, one of tyrosine (Tyr) and the other one is phenylalanine (PA) intermediates. Cinnamic acid is produced from PA by PA ammonia-lyase. The cinnamic acid is then hydroxylated with cinnamic acid 4-hydroxylase (C4H) to p-coumaric acid. Finally, cinnamic acid can be converted to RSV via 4-coumaryl-CoA lyase-1 (4CL1) and stilbene synthase (STS) (17). In the Tyr pathway, p-coumaric acid is formed by Tyr ammonium lyase from Tyr. Then it is condensed by the 3-malonyl-coA unit, and RSV is synthesized via 4CL1 and STS, such as the PA pathway in Figure 2 (18,19).

RSV is extensively metabolized by enzymes localized in the gut. Therefore, it shows a low oral bioavailability as a result of presystemic elimination. In the last decade, various methodological approaches (encapsulation, lipid nanocarriers, emulsions, etc.) have been developed to improve the low bioavailability of RSV (20).

Metabolism of RSV

The cis and trans are forms found in our daily diet, and 3-O-beta-D-glycoside is the glycosylated form of RSV. Although a small amount of RSV is absorbed by the ileum, most are absorbed by the jejunum. RSV enters the bloodstream after absorption by transmembrane transporters such as integrins or passive diffusion in the intestine and can exist in three different forms: Glucuronide, sulfate, or free form (21). It is modified by glucuronidation reaction in liver microsomes and reaches tissues. It is

Table 1. Resveratrol contents of foods

Foods	Resveratrol contents
Grape	6.47 µg/g d.m.
Grape seed extract	5.89 µg/g d.m.
Grape skin extract	3.54 µg/g d.m
Grape skin	50-100 µg/g
Grape juice	0.45-2.60 mg/L
Fresh grapes	0.16-3.54 µg/g
Raisin skin	24.06 µg/g
Red wine	0.362-1.979 mg/L
White wine	0.057-0.390 mg/L
Peanut and pistachios	0.02-1.79 µg/g
Raw peanuts	0.09-0.30 µg/g
Roasted peanuts	0-0.13 µg/g
Peanut butter	0.27-0.70 µg/g
Plum peel	0.1-6.2 µg/g
Tomato peel	18.4±1.6 µg/g d.m.
Black mulberry extract	50.61 µg/g d.m.
Lingonberry	5.88 µg/g d.m.
Cocoa	1.85±0.43 µg/g
Dark chocolate	0.35±0.08 µg/g
Chocolate milk	0.10±0.05 µg/g

d.m.: Dry matter

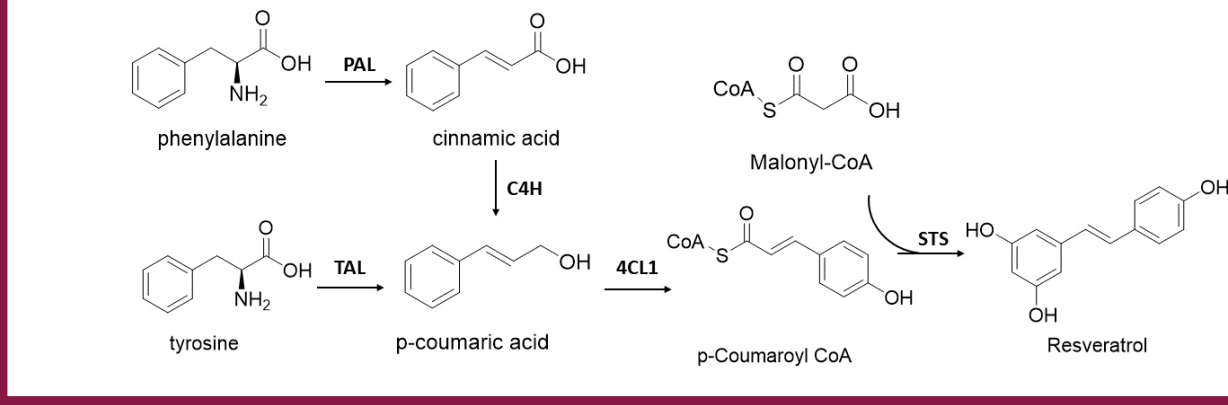


Figure 2. Biosynthesis of resveratrol
PAL: Phenylalanine ammonia-lyase, TAL: Tyrosine ammonium lyase, C4H: Cinnamic acid 4-hydroxylase, 4CL1: 4-coumaryl-CoA lyase-1, STS: Stilbene synthase

removed from the body through feces and urine in Figure 3 (22,23).

The major metabolite of RSV in humans is the sulfated metabolite resveratrol-3-O-sulfate. Other sulfated metabolites include resveratrol-4′-O-sulfate and resveratrol-3-O-4-O-disulfate. Glucuronide metabolites include resveratrol-3-O-glucuronide and resveratrol-4-O-glucuronide (24). In a study, it was observed that glucuronides were the main metabolite in plasma with low dose (5-50 mg) RSV, while monosulfates were the main metabolite in plasma with high dose (≥250 mg) RSV (25).

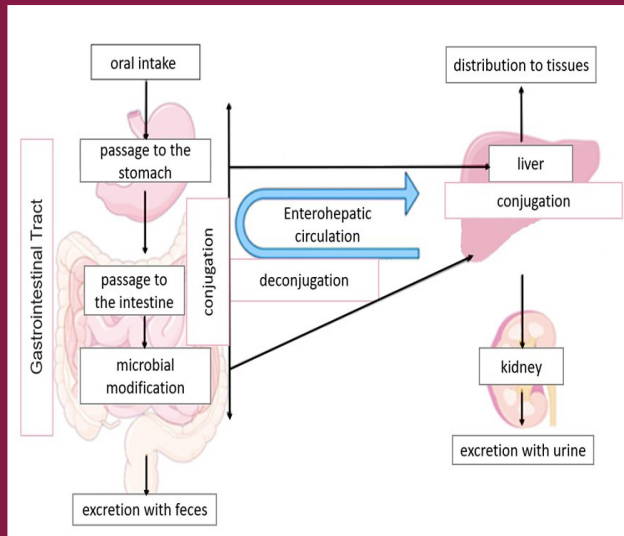


Figure 3. Metabolism and excretion of resveratrol

Pathophysiological Mechanism of RSV in Cancer

RSV has curative effects by investigating various *in vitro* and *in vivo* disease models, and this situation has ever increased the curiosity about RSV (26). At the same time, RSV targets and affects many molecules associated with human clinical conditions, such as cytokines, transcription factors, enzymes, and kinases (27). It has been observed that RSV shows anticancer activity by apoptosis, differentiation, and inhibiting cancer cell proliferation and prevents the neoplastic transformation of cells. In a study, it was shown that RSV prevents tumor angiogenesis, metastasis and also suppresses tumorigenesis phases (28). Many studies have been suggested that RSV acts apoptotic and anticancer effects on multiple cellular targets by controlling signaling pathways such as nuclear factor erythroid-2 (Nrf2), nuclear factor kappa B (NF-kB), sirtuin 1 (Sirt1), and 5'AMP-activated protein kinase (AMPK) in Figure 4 (29,30).

Modulates Apoptosis and Autophagy with Anticancer Effect

RSV plays a decisive role in cancer initiation, progression, and survival of cancer cells through modulation of apoptotic and autophagic cell death pathways (31). It activates the apoptosis mechanism by inducing the caspase enzyme system, which also regulates the expression and activity of the Atg5-Atg12-Atg16 complex required for the phagophore (32). RSV can directly activate Sirt1 expression and induce autophagy independently or dependently on the mammalian target of rapamycin (mTOR) (33). Sirt1 participates in many disease processes, including cancer and altered cellular metabolism disorders, while mainly modulating autophagy signaling. The activity of Sirt1 has an inverse relationship with mTOR (34). Moreover, Sirt1 can induce autophagy by affecting *Atg 5*, *Atg 7*, and *LC3* genes (35).

Mitogen-activated protein kinase (MAPK) is an essential regulator for the body, which is stimulated under stress and positively changes the response of cancer cells to targeted therapies and chemotherapy (36). MAPK modulates apoptosis by p38 kinase, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNKs) pathways (37). Which is a substantial signaling pathway in tumor migration and invasion, MAPK/NF-kB is suppressed by RSV (38). Another study on rats supported that RSV reduced metastasis through this pathway (39).

Effective on Metastasis

Today, its known that epithelial-mesenchymal transition (EMT) is associated with cancer progression, invasion, and metastasis. Studies have been shown that RSV can suppress the spread and metastasis of the tumor by increasing the invasiveness of cancer cells and inhibiting the signaling pathways associated with EMT, which is claimed to be a causative agent of metastasis (40). In addition, recent *in vitro* studies have suggested that different doses of RSV can be used as a therapeutic agent by demonstrating its therapeutic properties in many different cancer types such as oral squamous cell carcinoma, colorectal, prostate, and breast cancer via EMT (41,42).

RSV Inhibits Angiogenesis

Tumor angiogenesis is modulated by angiogenic stimulants, including vascular endothelial growth factor (VEGF), an important regulatory factor in the prognosis of various cancers (43). Hypoxia-inducible factor (HIF)-1α expression increases due to a deficiency in the oxygen microenvironment, which is closely related to the development and formation of various tumor types. HIF-1α also participates in angiogenesis considerably (44). HIF-1α interact with each other to regulate VEGF expression. Due to the therapeutic potential, RSV suppresses tumor angiogenesis by inhibiting HIF-1α and VEGF protein (45). In a study, RSV 800 mg/day was given to the participants orally for 40 days. As a result, it was observed that there was a decrease in the expression of *VEGF* and *HIF-1* genes with the effect of RSV in granulosa cells (46).

Its known that the hedgehog (Hh) signaling pathway can be involved in different tumors such as pancreatic and esophageal cancers, various stages of carcinogenesis, metastatic tumors, and stimulate tumorigenesis (47). It has been determined that RSV inhibits tumor formation and metastasis by suppressing the Hh signaling pathway (48).

Modulates Inflammation-related Cancer

Cancer formation is closely related to both chronic and acute inflammation processes. The presence of inflammation can cause tumor formation and progression, neoplastic transformation, and metastasis (49). A study showed that RSV had antioxidant and antiinflammatory activities with curative effects on carcinoma by modulation of STAT3/NF-kB and Nrf2/HO-1 signaling pathways (50). STAT3 is a key

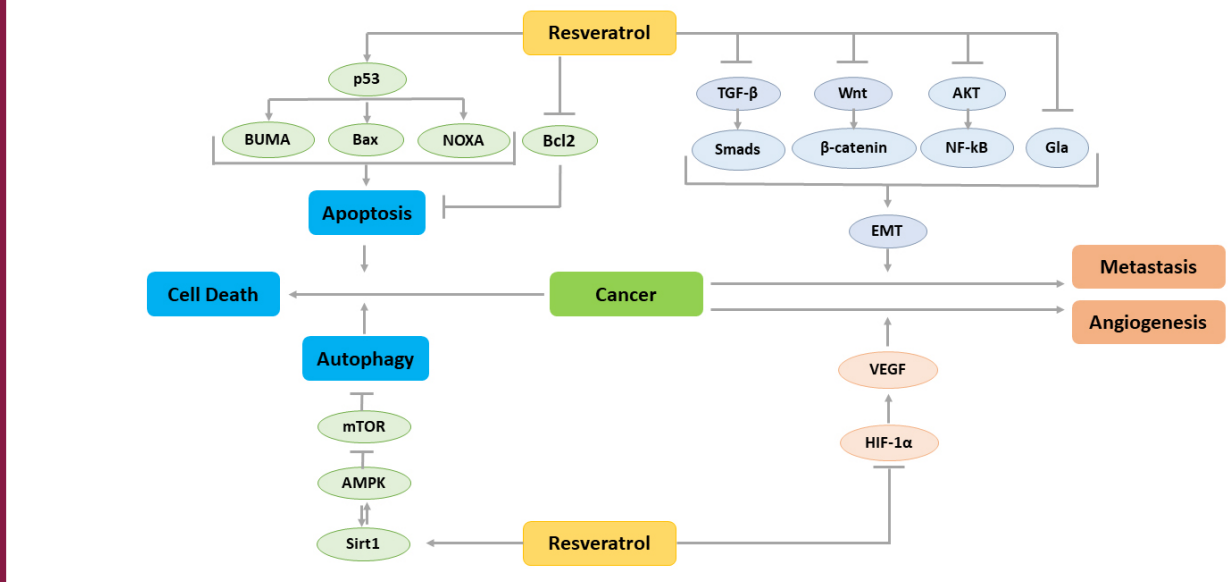


Figure 4. The relationship of resveratrol with apoptosis, autophagy, and cell death by affecting various signaling pathways

mTOR: Mammalian target of rapamycin, EMT: Epithelial-mesenchymal transition, VEGF: Vascular endothelial growth factor, AMPK: 5'AMP-activated protein kinase, Sirt1: Sirtuin 1

regulator of cell proliferation, apoptosis and is constitutively activated in cancer types. STAT3 is constitutively activated in many tumor types. Studies have shown that RSV effectively prevents cancer by inhibiting STAT3 expression (51). It also has an inhibitory effect on antiapoptotic mediators such as NF-kB, COX-2, phosphatidylinositol 3-kinase (PI3K), and mTOR (52). Activation of the Nrf2/antioxidant response element (ARE) pathway by endogenous or exogenous stimuli under normal physiological conditions has the potential to inhibit cancer and/or cancer cell survival, growth, and proliferation (53). RSV can inhibit tumorigenesis by regulating the expression of proteins, oxidase, and phase II detoxifying enzymes, which are of great importance in preventing tumorigenesis and activating the Nrf2/ARE signaling pathway (54). In addition, it can positively affect autophagy through the Nrf2/Keap1/p62 pathway and helps to regulate cellular homeostasis (55). RSV shows its anticancer effects through different mechanisms, one of which is inducing apoptosis of cancerous cells by activating apoptotic pathways via caspase proteins and programmed cell death (56). As a result of inflammation, various immune cells, such as neutrophils, macrophages, lipid cells, dendritic cells, and the release of cytokines and chemokines trigger the generation of cancer cells and cause the formation of the tumor microenvironment and tumor tissues by various pathways (57). Studies have been shown that the NLR family pyrin domain containing 3 (*NLRP3*) inflammasome gene, which is one of these pathways, plays a role in tumorigenesis. Activation of caspase-1, depending on the activation of the *NLRP3* gene causes the release of interleukin-18 (IL-18) and interleukin-1beta (IL-1β), resulting in oncological signals. Sirt1 protein is known to attenuate *NLRP3* inflammasome gene-dependent inflammation and pyroptosis through metabolic modulation. RSV downregulates the *NLRP3* gene by activating the Sirt1 protein, thereby inducing autophagy (58). In a study, it has been observed that RSV has an anti-tumor effect by suppressing the activity of NLRP3 in renal cancer cells (59).

Inhibiting Cancer Formation by Regulating Oxidative and Genotoxic Stress

Oxidative stress, which is defined as the imbalance between the increase in ROS production and the capacity of antioxidant systems to scavenge free radicals, is considered to strengthen carcinogenesis (60,61). However, RSV has a critical role as an antioxidant due to its ability to inhibit lipid peroxidation induced by the Fenton reaction, scavenging oxidants and free radicals, reducing oxidative reactions, and increasing the activity of antioxidant enzymes (62). RSV can improve the clinical outcome of certain cancers by downregulating COX-2 expression by acting on the NF- kB and activator protein-1 (AP-1) complex transcription factors with the aid of kinases such as MAPK/ERK/p38/JNK as a cancer preventative (63,64).

While antioxidants reduce oxidative stress at low doses, they have therapeutic doses that can increase the selective death of cancer cells and the effectiveness of standard treatment by increasing ROS production with a prooxidative effect at high doses (65). Studies have been shown that RSV at different concentrations offers favorable suppression of cancer generation and cancer treatment as RSV mediates cytotoxicity in cancer cells by increasing intracellular hydrogen peroxide (H_2O_2) and oxidative stress levels that will cause cell death (66). Its also known that RSV inhibits constitutive cyclooxygenase-1 but is not inducible to COX-2. Cyclooxygenases stimulate cell proliferation by producing prostaglandins from arachidonic acid, and tumor growth by angiogenesis and immunosuppression. Its thought that they can be used as therapeutic agents against various cancers by inhibiting cyclooxygenases (67).

The p53 protein has an important role in cell cycle arrest in response to genotoxic stress and inhibiting the development of carcinogenesis by inducing apoptosis (68). Studies have been affirmed that RSV activates p53, increases the expression of PUMA and BAX by activating an unknown signal pathway in addition to the p53-dependent pathway, and facilitates apoptosis by regulating the transcription of target genes involved in DNA repair (69). Similar to some chemotherapeutic drugs and radiotherapy, RSV induces DNA damage in cancer cells. Various cell death initiating enzymes are activated through signaling pathways by accumulating unrepaired DNA breaks in targeted cancer cells (70).

Conclusion

RSV is an ascendant compound that is effective in signal transduction pathways in the formation, development, and invasion stages of cancer cells. Its seen that RSV has anticancer effects with many mechanisms and signaling pathways. Account of all these properties, its thought to be a promising agent in the treatment of cancer disease. In order to benefit from its protective effects, foods containing RSV such as grapes, strawberries, blueberries, peanuts, and cocoa should be included in the diet. In addition to all these beneficial effects, its also known that RSV has side effects due to excessive intake. However, research is insufficient despite many studies on RSV and its effects on cancer. New studies are needed to explain this relationship and even to reveal the possible unknown beneficial effects of RSV.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Literature Search: B.N.Ö., E.M.G., Writing: B.N.Ö., E.M.G.

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