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REVIEW PAPER

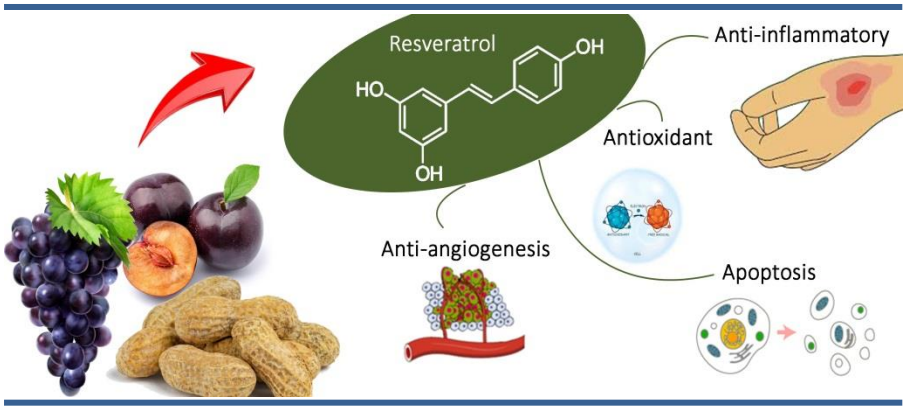
Potential therapeutic effects of herbal drug resveratrol against cancer

Danial Kahrizi
Department of Plant Production and Genetics, Faculty of Agriculture, Razi University, Kermanshah, Iran

Highlights

- Resveratrol could be a good candidate for cancer treatment.
- Resveratrol may overcome cancer by interfering with antioxidant pathways.
- Resveratrol can interfere with pathways associated with apoptosis.

Graphical Abstract



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Abstract

Cancer is a major global problem that faces many therapeutic challenges. Drug resistance can be an important problem in cancer treatment with chemotherapy. The use of plant-based compounds that have anti-cancer properties has recently been considered in the fight vs. cancer. One of these compounds is the natural substance resveratrol, which has many biological effects on cancer prevention and cancer treatment. This substance exists in more than 70 plant types, including grapes, peanuts, berries, plums, etc. Resveratrol has had a wide range of pharmacological features in recent years. It seems that this drug combination can be involved in various cellular mechanisms. For example, this compound can affect the molecules involved in the oxidative stress pathway and thus have anti-cancer effects. This compound can also affect molecules involved in the apoptosis pathway, affecting tumors. In addition, this compound has anti-angiogenic properties, which is a clear anti-cancer property. However, Resveratrol could be a suitable candidate in the treatment of cancer. In this review, we describe the therapeutic properties of Resveratrol in cancer based on its molecular mechanisms.

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*Corresponding author: dkahrizi@yahoo.com (D. Kahrizi)

Introduction

Resveratrol, with the formal name of E-5-(4-hydroxystyryl)benzene-1,3-diol, is known as a polyphenolic compound and has two cis and trans isomers. In fact, the trans form of the molecule is more dominant and is involved in biological procedures, including inhibition of cell proliferation, apoptosis, differentiation, and cell cycle (1). Researchers are studying the chemical properties of Resveratrol from different angles. As mentioned, Resveratrol has two isomers, cis- (Z) and trans- (E), and the trans isomer is changed to cis isomer under ultraviolet light. The predominant form of Resveratrol, if it is in powder form, can maintain its stability in the presence of air, the temperature of 40 degrees Celsius, and humidity of 75%. Modified resveratrol structures, including halogenated, hydroxylated, and methoxylated structures, have become an important research field for scientists. These modified structures, of course, all have propre therapeutic potential (2). Piceid is the glycosylated form of Resveratrol used in the food industry. This glycosylated form of Resveratrol protects its structure against the oxidizing enzymes of polyphenols. As a result, Resveratrol is protected from oxidation and thus inactivation by glycosylation and can exert its biological activity (3).

In some invasive plants, there are three analogues for glycosylated Resveratrol, including resveratroloside, piceatannol glucoside and piceid, which have high antibacterial properties (4). These glycosylated compounds must lose their glucose composition in order to pass through the intestinal epithelial cells, and as a result, they will have good biological effects. Glycosylated compounds have been shown to be even more efficient than Resveratrol. For example, piceid and Resveratrol are the same in terms of antioxidant potential, but for some reason, piceid seems to be more effective than resveratrol (5, 6). Also, in the face of the hepatitis B virus, Resveratrol is less effective than the glycosylated form of Resveratrol (7). In addition, the composition of Piceatannol is known for its properties such as protein-tyrosine kinase inhibitory, anti-leukemia, anti-leishmanial, cell proliferation, immune modulation, and strong anti-inflammatory (4). In this regard, converting Resveratrol to nano resveratrol can be a good way to ensure biological function. Such a form of Resveratrol increases its antioxidant activity as well as its solubility compared to the non-nanoform of Resveratrol (6).

Recent experimental studies, which are numerous, show that the drug resveratrol has a key effect on cancer cells. These anti-tumor effects of Resveratrol can be dose or treatment-way dependent. Numerous cellular mechanisms can be affected by this plant compound, the most important of which is the induction of apoptosis, anti-inflammation, anti-angiogenesis, and etc. (Figure 1). However, the exact mechanisms of Resveratrol's impacts on cancer cells have not been fully elucidated. The aim of this review was to assess the therapeutic effects of Resveratrol as a natural anti-cancer drug.

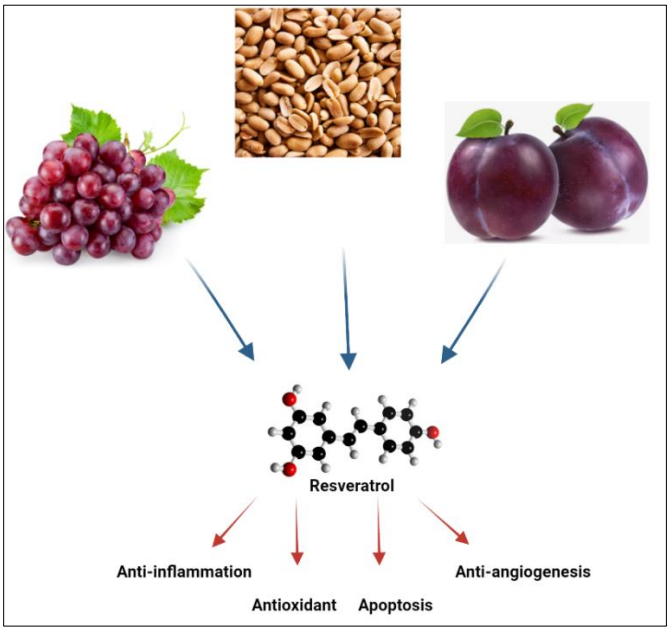

Figure 1. Resveratrol source and anti-cancer impacts.

Resveratrol exists in plant sources berries, grapes, peanuts, fruits, and some other plant origins and it could affect angiogenesis, apoptosis, inflammation, and oxidative stress pathways.

Antioxidant features of Resveratrol

Reactive oxygen species (ROS) are produced by the body's natural use of oxygen and by processes such as cell immune function as well as respiration. Free radicals such as hydroxyl, superoxide anion, as well as some non-free radical compounds such as hydrogen peroxide are considered ROS. These radicals are normally produced by normal cell processes in the body and may oxidize membrane lipids and initiate the accumulation of lipid peroxides. At physiological concentrations, ROS is required for some cellular functions. But at high concentrations, they can destroy biomacromolecules such as carbohydrates, proteins, lipids, and nucleic acids. If this condition persists and the antioxidant system fails to help eliminate ROS, the diseases will eventually develop (8, 9).

Organisms that breathe aerobically use antioxidant enzymes or antioxidant nutrients to repair created damage to macromolecules by oxidative stress. These compounds can remove ROS, stop lipid peroxidation, and ultimately increase cell life. Therefore, the presence of antioxidants to protect the body against ROS seems to be essential, which in turn can prevent chronic diseases. However, it is essential to find antioxidants with natural resources, especially of plant origin, as an alternative to antioxidant nutrients. These natural antioxidants can prevent chain oxidation processes. Recently, the usage of antioxidants, including tert-butyl hydroquinone, propyl gallate, butylated hydroxytoluene (BHT), and butylated hydroxy anisole (BHA) has become common. However, the use of butylated hydroxy anisole and butylated hydroxytoluene has been limited due to the potential for carcinogenicity and toxicity. So, there is a strong tendency to use natural yet safe antioxidants (10, 11). Many plant-based foods contain non-flavonoid phenolic compounds that are made by plant cells. Among these compounds, Resveratrol may have a positive effect on physiological functions. This compound is found in grapes, berries, peanuts, fruits, and some other plant sources. Due to the fact that this combination can have a good impact on human health, it has received a lot of attention.

Resveratrol activity has been extensively evaluated experimentally. The benefits of this combination include improved atherosclerosis and blood flow. This combination can improve cardiovascular function, which is possible by eliminating oxidative stress, preventing platelet aggregation, and improving vasodilation. This plant compound can also have an inhibitory effect on various stages of tumor formation, including its onset and progression. The influence of Resveratrol on inhibiting cell proliferation has been revealed to be a dose-dependent process. This combination can also be used in the treatment of skin and liver diseases (12, 13). It is possible that the positive impacts of Resveratrol may be due to the increase in high-density lipoprotein cholesterol, inhibition of platelet aggregation, stimulation of nitric oxide synthesis and its antioxidant properties. All of these properties could make Resveratrol a cardioprotector. It also has antiviral, neuroprotective and anti-inflammatory properties (14).

Resveratrol as an anti-inflammatory agent

The complex process of inflammation involves several stages that involve many cells and mediators. This process is an adaptive response that is caused by certain factors such as tissue damage or invasion of microorganisms. Therefore, the source of inflammation can be endogenous or exogenous (15). Various experimental studies have shown that Resveratrol can inhibit anti-inflammatory agents and thus overcome inflammation. Resveratrol prevents the generation of TNF-α and interleukin-12 by acting on macrophages. It can also affect lymphocytes and prevent the generation of interferon-gamma and IL-2. In addition, they prevent the spleen cell proliferation stimulated by Alloantigens, IL-2, and concanavalin A (16). Also, Resveratrol has been shown to inhibit the production of tumor necrosis factor-alpha, IL-1α, and IL-6, as well as reduce IL-17 expression at the level of mRNA and protein (17). In vivo conditions, Resveratrol upregulates the expression of proteins contributed to tight junctions, including claudin-1, occludin, and occludens-1, which in turn affect

these connections in the intestine and reduce its permeability (18, 19). It also improves kidney function by reducing inflammatory factors including NOX4, NF-kB, and NADPH (20). A specific precursor, Resveratrol, reduces inflammation in conditions of infection with Mycoplasma gallisepticum, and exerts this by reducing the expression of tumor necrosis factor-alpha, IL-1β, and IL-6 (21).

Also, it has been shown that Resveratrol has an anti-inflammatory effect in an animal model of carrageenan-induced paw edema as an acute inflammation model (22). In addition, Resveratrol has been shown to improve cerebral ischemia in rats by modulating inflammation in the hippocampus. Resveratrol can also inhibit neuroinflammation and protect neurons from inflammatory damage. In addition, this compound can eliminate asthma-induced respiratory inflammation (23-25). The gram-negative bacterial endotoxin contains a component called lipopolysaccharide that can induce inflammatory responses. Resveratrol reduces some inflammatory mediators such as TNF-α, IL-8, IL-1β, COX-2 and prostaglandin E2 in lipopolysaccharide-treated cells (26, 27). A similar event occurred for the TLR-4 receptor in LPS-treated and Resveratrol pretreated cells (28). Also, in elderly animals, long-term treatment with Resveratrol improves anti-inflammatory function against lipopolysaccharide (29). Also, in C2C12 cells where TNF-α and IL-6 levels are stimulated by palmitate, the addition of Resveratrol inhibits the production of these inflammatory agents (30).

Also, the resveratrol compound exerts its anti-inflammatory features by inhibiting the generation of reactive oxygen species and nitric oxide. Oxidative stress created by ROS can result in the progress of inflammation and related diseases such as cancer (31). Nitric oxide produced in macrophages is inhibited by Resveratrol. Resveratrol is also able to reduce mRNA and nitric oxide synthase peptide levels (32). The protective effects of Resveratrol can also be attributed to the fight against mitochondrial ROS. As mentioned, Resveratrol is able to increase the activity of antioxidant enzymes, of which antioxidant enzymes include GPX, CAT, and SOD (33). An in vivo study found that Resveratrol can increase liver antioxidant and anti-inflammatory action in chronic depression by normalizing levels of myeloperoxidase, TNF-α, NF-κB, malondialdehyde, glutathione, and total antioxidant ability (34). One experiment also found that if intestinal cells were stimulated with lipopolysaccharides (LPS), Resveratrol could lower nitric oxide synthase levels and ultimately lower nitric oxide (28). Also, if RAW264.7 cells exposed to LPS are treated with Resveratrol, interleukin-6 and nitric oxide levels are reduced (35).

Induced apoptosis by Resveratrol

In cells, the mitochondrial organelle is recognized as a major basis of reactive oxygen species. In addition, this organ has a main role in the apoptosis process. Some studies have shown that mitochondrial ROS is induced in cancer cells, which can induce an apoptotic process if treated with Resveratrol (36). In some cancer cells, the induction of apoptosis is a mitochondrial-dependent process. In some cells, this process is independent of caspase signaling, while in others, it requires the cytochrome C release from the mitochondria and the activation of caspases. Treatment of SW480 cell line with Resveratrol releases cytochrome C from the mitochondrial membrane and induces apoptosis. Resveratrol can activate some miRNAs that have a vital role in inhibiting Bcl-2. Thus, Bax penetrates the mitochondria and apoptosis is activated. Such behavior has been detected with Resveratrol in breast tumor cells (36, 37).

Resveratrol has a dual function on mitochondria and in addition to the apoptotic process, can interfere with mitochondrial modulation to produce ROS, thus leading to the destruction of the mitochondrial genome and ultimately apoptosis of that cell. This compound can increase mitochondrial oxidative phosphorylation and also enhance the apoptosis process by ROS (38). With the help of Resveratrol, calcium ion flow can be promoted to the cytoplasmic level of the cell, which increases the activity of intracellular oxygen species, which is mediated by the TRPM2 receptor (39). In addition, this compound can cause apoptosis in cancer cells by accumulating calcium ions in the mitochondria (36, 40). The SIRT1 molecule is involved in regulating activities such as response to genome damage, apoptosis, and cell cycle. It is actually functionally associated to the p53 molecule, so it may be considered a tumor suppressor. Resveratrol can affect this molecule and inhibit the NF-κB signal

pathway, initiating apoptosis in colorectal cancer cells. This plant compound is also able to degrade NF-κB by activating SIRT1, which occurs through de-acetylation of the p65 molecule (41). Thus, Resveratrol can sensitize cancer cells and assist them in responding to chemotherapy and radiotherapy (42). Resveratrol in breast tumor cells is able to stimulate the differentiation process by the SIRT1 molecule. Also, by activating SIRT1, this drug combination can reduce the activity of PI3K, followed by a reduction in Bcl-2 and, finally an increase in apoptosis (36, 43).

Influence of Resveratrol on angiogenesis

Resveratrol may affect and prevent the angiogenesis procedure, a mechanism that has been detected in glioma, breast, and lung tumor cells (44). This molecule could prevent the procedure of chemotaxis and the growth of endothelial cells in capillaries through VEGF and bFGF receptors (45). Also, in chick chorioallantoic membrane, this molecule can increase the p53 molecule and increase apoptosis in bFGF-stimulated endothelial cells and thus block the angiogenesis process (46). In addition to having a straight influence on endothelial cells, Resveratrol can also inhibit the angiogenic process in vivo. This plant compound can cause endothelial cell apoptosis, inhibit VEGF, and inhibit angiogenesis in glioma cells. This anti-angiogenic effect of Resveratrol is evident at higher doses (47). Various laboratory studies have shown that Resveratrol blocks the inhibition of angiogenesis through several basic mechanisms. For example, it can participate in this process by interfering with the proliferation and migration of vascular smooth muscle cells and endothelial cells (48). Of course, other factors such as increased expression of p21 and p53 molecules, binding of bFGF to its receptor and blockage of VEGF expression, blocking COX-2 and some MMPs, etc. are also involved in this process (44).

Effects of Resveratrol against breast cancer

Examination of laboratory models has shown that Resveratrol can act against breast cancer. This model is created in different ways to study the effects of different substances in animal models of breast cancer. For example, carcinogens such as DMBA, estradiol, and N-methyl-nitrosourea are used to induce breast tumors. Either animal models with HER-2/neu overexpression or mutations in the Brca1 gene are also considered breast cancer models. Resveratrol inhibits N-nitoso-N-methylurea-induced tumors in rats (42, 49). In a specific animal model, the plant composition resveratrol was found to reduce angiogenesis and increase apoptosis. However, in another animal model, this substance had no effect on metastasis (50). Another animal study of breast cancer found that Resveratrol, in a specific dose and intraperitoneally, did not affect cancer cells. This result was referred to as the low dose of Resveratrol (51). But in another model, it was found that oral treatment of a specific animal model with Resveratrol could inhibit 4T1 and prevent lung metastasis (52).

Decreased expression and activity of MMP-9 were evident in the anti-cancer effects of Resveratrol. However, the therapeutic influences of Resveratrol can depend on the kind of treatment as well as the dose (42). In other specific animal models in which breast cancer was specifically induced, the drug resveratrol decreased the expression of some genes involved in cell proliferation and survival, including β-catenin, PI3K, PCNA, etc. the anti-apoptotic protein Bcl-xL plays its anti-cancer role. Resveratrol can also increase p21 tumor suppressor protein and Bax apoptotic protein (Figure 2) (42). In addition, when Resveratrol was used orally in water as a supplement, it could act as an anti-cancer agent against breast tumors in HER-2/neu mice. This combination could reduce the number of tumors and their size and alter the expression of some genes (53).

Effects of Resveratrol against colorectal cancer

Some factors such as poor diet, alcohol consumption and smoking can lead to colorectal cancer. Animal genetic models of colorectal cancer, such as $Apc^{Min/+}$ and $Apc^{Pirc/+}$ rats, were also evaluated with the anti-cancer drug resveratrol. In addition, the colorectal tumor could be caused by substances such as azoxymethane as well as dextran sulfate sodium, 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine, and some other carcinogens (54). Colorectal cancer presents with some pathophysiological features such as adenoma, adenocarcinoma,

hyperplasia and aberrant crypt foci (55). In some of these carcinogen-induced cancer models, Resveratrol could overcome some of the features of colorectal cancer in rodents (42).

Resveratrol can alter the expression of some genes contributed to apoptosis, inflammation, and oxidative stress, including increased expression of Bax, p53, HO-1, Nrf2, and glutathione reductase. It also decreased the expression of NF-κB, PKC-β2, TNF-α, iNOS, and aldose reductase genes. The drug resveratrol in animal models treated with 1,2-dimethylhydrazine can modulate the histological and pathological features of colorectal cancer. This substance can cause enzymatic changes in colon cancer, which are enzymatic changes to improve cancerous lesions. For example, the activity of the antioxidant enzymes superoxide dismutase and catalase in the liver and intestine may be increased. The processing of enzymes such as mucinase, nitroreductase, β-galactosidase, β-glucuronidase, and β-glucosidase is also reduced in fecal samples. The drug resveratrol reduced the expression of genes including Mucin 1, COX-2, ODC, Hsp70, and Hsp27 in colonic mucosa. GSH levels in erythrocytes, plasma, intestine/colon, and liver were also increased (56-58). It is worth noting that in some genetically transgenic animal models, Resveratrol can prevent the progress of colon cancer (59).

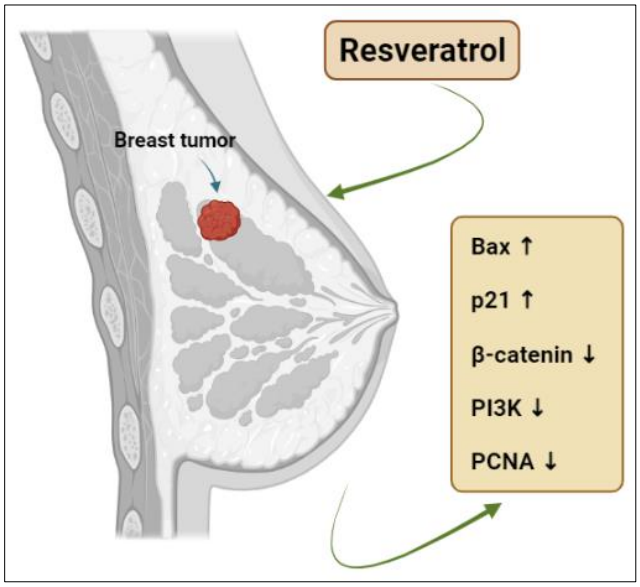

Figure 2. Effects of Resveratrol on the expression of some genes in breast cancer.

Resveratrol could affect some gene profiles for example, it increases the Bax and p21 gene expression while this compound decreases β-catenin, PI3K, and PCNA gene expression in breast cancer.

Prostate cancer and Resveratrol

The combination of Resveratrol can reduce adenocarcinoma in the prostate in a genetic animal model. This drug combination in a specific model of transgenic mice could reduce the expression of androgen receptors as well as kallikrein 11. These mechanisms can be adopted against prostate cancer. In another animal model of prostate cancer developed by PC-3 cell transplantation, oral resveratrol treatment overcame prostate cancer. This process was correlated with mechanisms including apoptosis induction, cell proliferation reduction, and tumor volume. In another study in mice with prostate cancer induced by DU-145 cells, Resveratrol was able to reduce tumor development as well as metastasis (60-65).

Resveratrol compound against lung cancer

In animal models, lung cancer can be induced by several factors. These substances include urethane, vinyl carbamate, uracil mustard, diethylnitrosamine, etc. In an animal study, chemically induced lung cancer could reduce specific adducts of DNA, improve histo structure, and reduce tumor size. It can also induce apoptosis by activating caspase-9 and 3 proteins. Of course, other anti-tumor processes are involved. These include

decreased serum LDH activity, impaired glucose uptake, and inactivation of the p53 molecule. Another mouse model also found that Resveratrol could be involved in xenograft cancer models (42, 66-68). The impacts of Resveratrol were not observed in Lewis lung carcinoma in mouse. However, it could affect the metastasis process and reduce it. Also, it could influence the number and weight of metastasis. In addition, it was detected that Resveratrol could alter the expression of some genes, including CYP1B1 and CYP1A1 (42, 69, 70).

Conclusion

Cancer has plagued many people for years and is the second leading cause of death after heart disorders. Cancer is a very complex disease with genetic, epigenetic, and environmental origins. This disease has a great variety in tissue, tumor, and cellular levels and this diversity can lead to inappropriate treatments. Current cancer treatments often include radiation, chemotherapy, and surgery to resect the tumor. So far, current treatments have been associated with side effects such as damage to healthy cells, drug resistance, and relapse. Therefore, achieving new solutions with more effectiveness and less toxicity and side effects is very important. In addition, various studies on people living in different environments show that nutrition has an important role in cancer risk. Therefore, in recent years, nutritional interventions and the use of various natural compounds in the diet in the field of cancer are considered. One of the herbal supplements that can be considered as a dietary supplement in the treatment of cancer is Resveratrol. This compound is a polyphenol that is found in many food sources. Since this combination has anti-inflammatory properties, induction of apoptosis, anti-angiogenesis, etc., it could be considered a suitable candidate for treating several cancers.

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