Natural Environmental Sources of Resveratrol and Its Therapeutic Role in Cancer Prevention

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Abstract

Resveratrol, a polyphenolic compound found in plants like grapes and berries, is gaining recognition for its potent anti-cancer, anti-inflammatory, and antioxidant properties. This review offers a comprehensive examination of resveratrol's role in cancer prevention and treatment, focusing on its ability to modulate key signaling pathways such as NF-κB, PI3K/Akt, and apoptotic regulators. Resveratrol also reduces oxidative stress by scavenging reactive oxygen species (ROS), contributing to its therapeutic potential. Despite its promise, challenges related to resveratrol's absorption, distribution, metabolism, and excretion (ADME) limit its clinical application. Recent advancements in drug delivery systems, including liposomes and nanoparticles, have shown potential to improve its bioavailability and therapeutic efficacy. This review also addresses the compound's safety, toxicity profiles, and interactions with other cancer therapies. Preclinical studies reveal resveratrol's preventive efficacy, with findings suggesting reductions in the risk of breast and colon cancers by 60–80% through inhibition of precancerous lesions. Additionally, emerging research highlights resveratrol's synergistic effects when used alongside chemotherapy and radiotherapy, enhancing treatment outcomes. Future research should prioritize large-scale clinical trials to optimize dosage, evaluate the long-term safety, and explore innovative delivery methods to realize resveratrol's therapeutic potential in cancer carefully. Resveratrol stands as a promising agent in cancer prevention and treatment, warranting further investigation into its clinical applications.

Keywords: Resveratrol, cancer prevention, apoptosis, bioavailability, signaling pathways.

Significance | Resveratrol's potential in cancer therapy highlights its importance as a promising adjunct treatment, improving efficacy and reducing side effects.

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Editor Muhammad Asif, Ph.D, And accepted by the Editorial Board Jul 21, 2024 (received for review Apr 07, 2024)

1. Introduction

Resveratrol, a polyphenolic compound predominantly found in grapes, berries, and peanuts, has gained significant attention for its potent anti-cancer properties. It is a naturally occurring stilbene, recognized for a variety of beneficial health effects beyond its anticancer potential, including anti-inflammatory, antioxidant, and anti-diabetic activities (Baur & Sinclair, 2006; Tufael et al., 2024). This compound's wide range of bioactivities, particularly its role in cancer prevention and treatment, has led to an extensive body of research focusing on its molecular mechanisms and therapeutic potential. These mechanisms involve the modulation of several key cellular pathways implicated in cancer progression, such as the nuclear factor-kappa B (NF-κB), phosphoinositide 3-kinase (PI3K)/Akt, and apoptotic regulators (Sabra et al., 2021). Resveratrol has been shown to sensitize cancer cells to

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Please cite this article.
Md Rahedul Islam, Tamanna Yesmin et al. (2024). Natural Environmental Sources of Resveratrol and Its Therapeutic Role in Cancer Prevention, 7(1), 1-11, 9931

chemotherapy and mitigate drug resistance, making it a promising adjunct in cancer therapy (Anwar et al., 2023). Approximately 90–95% of genetic mutations leading to cancer are attributed to environmental factors, with inherited mutations accounting for only 5–10% (Kiskova et al., 2020). By targeting these environmentally induced mutations, resveratrol demonstrates broad-spectrum anticancer effects against various malignancies, including brain, lung, liver, and breast cancers (Sajadimajd et al., 2023). Its therapeutic efficacy has been linked to the ability to induce apoptosis, halt the cell cycle, and disrupt pathways critical for cancer cell survival.

Chemically, resveratrol exists in two isomeric forms, trans- and cis-resveratrol, with the trans-isomer being the most stable and biologically active form (Xie et al., 2023). Resveratrol is abundant in food sources such as red wine and grape skins, contributing to its bioavailability in the human diet (Xiao et al., 2019). However, despite its promising bioactive properties, resveratrol's clinical application faces challenges, primarily due to its poor absorption, rapid metabolism, and low bioavailability (Soleas et al., 1997). Addressing these limitations has become a focal point in recent research, with advancements in drug delivery systems like liposomes, nanoparticles, and chemical derivatives aimed at enhancing its therapeutic efficacy (Jo et al., 2022).

This review provides a comprehensive examination of the current state of research on resveratrol's cancer-preventive and therapeutic mechanisms. It covers the activation of key signaling pathways, the compound's role in scavenging reactive oxygen species (ROS), and the modulation of apoptotic regulators. Additionally, challenges related to resveratrol's pharmacokinetics absorption, distribution, metabolism, and excretion (ADME) are explored, along with recent strategies developed to overcome these hurdles. Safety, toxicity profiles, and adverse effects at different dosage levels are also addressed. Importantly, this review highlights the preventive efficacy of resveratrol, with evidence from preclinical studies showing significant reductions in breast and colon cancer risk. Lastly, the potential for resveratrol to enhance bioavailability through novel drug delivery systems and its synergistic effects with conventional cancer therapies are discussed, underscoring the need for large-scale clinical trials to validate these findings across diverse patient populations.

2. Chemical Structure and Sources of Resveratrol

Resveratrol, chemically known as 3,4′5-trihydroxystilbene, is a naturally occurring polyphenolic compound found in various plants. This molecule exists in two isomeric forms: cis and trans, with the trans form being the more biologically active. Structurally, resveratrol belongs to the stilbene family, which is characterized by two aromatic phenolic rings connected via an ethylene bridge, a structure that imparts resonance stability (Islam et al., 2024). This unique structure enhances its interaction with reactive oxygen species (ROS), contributing to its potent antioxidant activity, as illustrated in Figure 1.

The main natural sources of resveratrol include the skins of grapes, berries, and the roots of Japanese knotweed (Polygonum cuspidatum), where it acts as a phytoalexin, a defense molecule produced in response to stress or infection (Malviya et al., 2022). Due to its high concentration in red wine, resveratrol has gained attention for its potential role in the "French Paradox," a term used to describe the lower incidence of coronary heart disease in France despite a diet rich in saturated fats, likely attributable to moderate wine consumption.

Chemically, resveratrol's functional groups include hydroxyl (-OH) moieties that contribute to its antioxidant and anti-inflammatory properties (Bala et al., 2023). These hydroxyl groups are crucial in scavenging ROS and mitigating oxidative stress, which can damage cellular components and contribute to chronic diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders. Furthermore, resveratrol is known for its pleiotropic effects, influencing multiple cellular pathways and offering therapeutic benefits across a range of diseases (Tufael., 2022).

Despite its potential, the bioavailability of resveratrol remains a challenge due to rapid metabolism and low absorption in humans (Koushki et al., 2018). Efforts to overcome these limitations include chemical synthesis and microbial fermentation. One innovative method involves fermenting grape musts with specific yeast strains in methanol or ethanol, followed by chromatographic purification, achieving resveratrol purity of up to 99%. Such approaches are critical for producing resveratrol in commercial quantities while maintaining its therapeutic potential.

3. Mechanisms of Resveratrol in Cancer Prevention

Resveratrol exhibits multiple mechanisms of action in cancer prevention, including inducing apoptosis, modulating cellular signaling pathways, inhibiting metastasis and angiogenesis, and exerting potent antioxidant effects.

3.1 Antioxidant Activity

Resveratrol's ability to neutralize free radicals positions it as a potent antioxidant that can help prevent cancer development. By scavenging reactive oxygen species (ROS), resveratrol reduces oxidative stress, protecting cellular DNA from damage that could lead to mutations and the initiation of cancer (Kumar et al., 2022). Several studies demonstrate resveratrol's role in enhancing antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), which are essential for eliminating ROS and preventing oxidative DNA damage. The work of Fukuoka et al. (2023) highlights the increased expression and activity of these enzymes upon resveratrol treatment, supporting its role in cancer chemoprevention. Elevated activity of SOD and CAT is crucial in mitigating ROS-induced oxidative damage, as noted by Leonard et al. (2003), reinforcing the protective role of resveratrol against DNA mutations.

Hirota et al. (2002) also demonstrated that resveratrol significantly reduces oxidative DNA damage, thus blocking the mutations that could drive carcinogenesis. Montalesi et al. (2023) further corroborate this by showing that resveratrol enhances cellular defense mechanisms against oxidative stress, which is a pivotal factor in its chemopreventive potential. Collectively, these studies suggest that resveratrol's antioxidant properties are integral to its ability to prevent the onset of cancer by boosting the cell's natural defenses against oxidative damage.

3.2 Modulation of Signaling Pathways

Resveratrol modulates several keys signaling pathways implicated in cancer cell proliferation and apoptosis. One of the most studied pathways affected by resveratrol is the nuclear factor-kappa B (NF-κB) pathway, which plays a central role in inflammation and cancer progression. Resveratrol inhibits NF-κB activation, leading to the suppression of pro-inflammatory cytokines and survival proteins commonly upregulated in cancer cells (Aggarwal et al., 2004). By downregulating these factors, resveratrol decreases the transcriptional activity of genes responsible for inflammation and anti-apoptosis, both of which are critical for cancer cell survival.

In addition to the NF-κB pathway, resveratrol regulates the phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways. The PI3K/Akt pathway, which regulates cell growth and survival, is inhibited by resveratrol, resulting in reduced phosphorylation of key proteins and induction of apoptosis in cancer cells (Van Ginkel et al., 2007). Similarly, the MAPK pathway, which responds to extracellular stimuli, is modulated by resveratrol, leading to reduced cell proliferation and increased apoptotic signaling.

Resveratrol also inhibits the Wnt/β-catenin signaling pathway, which is involved in cell proliferation, migration, and tumor progression. By reducing nuclear β-catenin levels and downregulating Wnt target genes, resveratrol suppresses tumor growth and metastasis (Flourakis et al., 2010). Moreover, its impact on the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway is significant, as activation of AMPK by resveratrol leads to mTOR inhibition, reducing protein synthesis and triggering apoptosis through mitochondrial swelling (Baur & Sinclair, 2006).

Lastly, resveratrol affects the Notch signaling pathway, which is critical for cell differentiation and survival. Downregulation of Notch1 and its associated genes by resveratrol has been linked to suppressed proliferation and increased apoptosis in cancer cells, providing further evidence of its anticancer potential (Rizzo et al., 2014).

Through its multifaceted effects on signaling pathways and its potent antioxidant properties, resveratrol represents a promising candidate for cancer prevention and therapy.

3.3 Induction of Apoptosis

Resveratrol plays a critical role in inducing apoptosis, a process of programmed cell death, which is a promising therapeutic strategy for targeting rapidly dividing cancer cells. Apoptosis can occur through two primary pathways: the intrinsic (mitochondrial) and the extrinsic (death receptor-mediated) pathways. Resveratrol exerts its pro-apoptotic effects by influencing both.

In the intrinsic apoptotic pathway, resveratrol modulates the balance between pro-apoptotic and anti-apoptotic proteins. It upregulates the expression of pro-apoptotic proteins such as Bax, which promotes mitochondrial outer membrane permeabilization, leading to the release of cytochrome c into the cytosol (El-Readi et al., 2019). Cytochrome c, in turn, triggers the formation of the apoptosome complex, which activates caspase-9 and subsequently caspase-3, executing apoptosis. Concurrently, resveratrol downregulates anti-apoptotic proteins like Bcl-2, shifting the balance in favor of cell death (El-Readi et al., 2019). By disrupting mitochondrial integrity, resveratrol enhances apoptosis, making it a powerful agent against cancer cells that rely on mitochondrial function for survival.

The extrinsic apoptotic pathway is initiated by the interaction of death receptors on the cell surface with their corresponding ligands. Resveratrol has been shown to increase the expression of death receptors such as Fas (CD95) and death receptor 5 (DR5) on the surface of cancer cells (K. B. Singh et al., 2018). Upon ligand binding, these receptors activate caspase-8, which then directly activates downstream effector caspases like caspase-3, leading to apoptosis (Jeong et al., 2019). Additionally, resveratrol can potentiate the effect of BH3 mimetics small molecules that inhibit Bcl-2 proteins thereby further enhancing apoptosis in resistant cancer cells ("Retraction," 2021).

Furthermore, resveratrol sensitizes cancer cells to apoptosis by inhibiting survival pathways such as the PI3K/Akt signaling pathway. The PI3K/Akt pathway is commonly activated in many cancer types and promotes cell survival, proliferation, and resistance to apoptosis (Jiang et al., 2009). By inhibiting this pathway, resveratrol reduces the survival signals within cancer cells, making them more prone to apoptotic death. This dual activation of both intrinsic and extrinsic apoptotic pathways underscores resveratrol's potential as a powerful anticancer agent that can target multiple vulnerabilities in cancer cells.

3.4 Inhibition of Metastasis and Angiogenesis

In addition to inducing apoptosis, resveratrol has demonstrated significant potential in inhibiting cancer metastasis and angiogenesis, which are essential processes for tumor progression and spread.

Metastasis involves the ability of cancer cells to invade surrounding tissues and migrate to distant organs. This process is facilitated by enzymes such as matrix metalloproteinases (MMPs), which degrade the extracellular matrix (ECM) and allow cancer cells to invade new tissues. Resveratrol has been shown to inhibit the expression and activity of key MMPs, including MMP-2 and MMP-9, which are critical for tumor cell invasion (Cheng et al., 2019). By preventing ECM breakdown, resveratrol reduces the ability of cancer cells to metastasize, thus limiting their spread to distant organs. This inhibition of metastasis is a crucial aspect of resveratrol's anti-cancer action, particularly in cancers that are prone to rapid dissemination, such as breast and colon cancers.

Angiogenesis, the formation of new blood vessels, is another critical process in cancer progression. Tumors require a blood supply to receive oxygen and nutrients necessary for their growth and survival. Resveratrol exerts anti-angiogenic effects by downregulating vascular endothelial growth factor (VEGF) and its receptors (VEGFR) (Cheng et al., 2019). VEGF is a key pro-angiogenic factor that stimulates the growth of new blood vessels, facilitating tumor expansion. By inhibiting VEGF signaling, resveratrol prevents the formation of new blood vessels, thereby starving the tumor of essential resources and limiting its growth. This dual action reducing both metastasis and angiogenesis makes resveratrol a potent inhibitor of cancer progression.

Studies supporting resveratrol's role in inhibiting metastasis and angiogenesis have been conducted across various cancer models, demonstrating its broad-spectrum anti-cancer potential. The inhibition of MMPs and VEGF further highlights resveratrol's capacity to disrupt key processes that tumors exploit to grow and spread. As such, resveratrol holds promise as part of a comprehensive strategy for cancer therapy, particularly when used in combination with other agents to enhance its efficacy.

4. In Vitro Studies

In vitro studies have consistently demonstrated resveratrol's significant anticancer effects, showcasing its ability to inhibit cancer cell proliferation, induce apoptosis, and modulate key signaling pathways involved in cancer development and resistance to chemotherapy.

A landmark study by (Kar et al., 2024) was among the first to reveal resveratrol's anticancer potential. This study demonstrated that resveratrol inhibits the proliferation of breast cancer cells by modulating estrogen receptor (ER) activity, positioning resveratrol as a phytoestrogen with the potential to target hormone-dependent cancers. This finding has had significant implications for the development of therapeutic strategies for estrogen-positive cancers, such as breast and ovarian cancers.

Subsequent studies explored the broader mechanisms through which resveratrol induces apoptosis across various cancer types. Hsieh and Wu (1999) provided evidence that resveratrol promotes apoptosis in prostate cancer cells through a caspase-independent pathway. This process involves the regulation of pro-apoptotic proteins, such as Bax and Bad, and the downregulation of anti-apoptotic proteins, like Bcl-2. This caspase-independent mechanism expands the understanding of resveratrol's ability to induce cancer cell death without solely relying on the caspase family of enzymes, which are often downregulated in resistant cancer cells. This further supports the chemopreventive potential of resveratrol across different malignancies.

In addition, research by Fulda (2010) demonstrated that resveratrol activates apoptotic pathways in colon cancer cells by downregulating anti-apoptotic proteins and upregulating pro-apoptotic markers. Fulda's study illustrated that resveratrol effectively triggers the intrinsic apoptotic pathway in colon cancer, highlighting its potential as a treatment for gastrointestinal cancers, where chemoresistance is a significant challenge.

Another critical finding in the study of glioblastomas (highly aggressive brain tumors) demonstrated resveratrol's ability to arrest cancer cells in the G1 phase of the cell cycle. Lu et al. (2010) found that resveratrol inhibits the PI3K/Akt signaling pathway, a critical survival mechanism for glioblastoma cells. By reducing the activity of this pathway, resveratrol decreases cancer cell proliferation and enhances sensitivity to apoptotic signals, making it an attractive candidate for glioblastoma therapy, where current treatments often fail to effectively target this pathway.

Additionally, resveratrol has been shown to influence the Wnt/β-catenin signaling pathway, which is heavily implicated in colorectal cancer. Cai (2011) reported that resveratrol inhibits this pathway, reducing tumorigenic potential and preventing cancer cell proliferation. This suppression of Wnt/β-catenin signaling is significant, as aberrations in this pathway are a hallmark of many colorectal cancers, suggesting that resveratrol could be beneficial as part of a targeted treatment strategy for colorectal cancer patients.

These in vitro studies have provided valuable insights into the molecular mechanisms by which resveratrol exerts its anticancer effects. By targeting multiple signaling pathways such as the estrogen receptor, PI3K/Akt, and Wnt/β-catenin pathways resveratrol has demonstrated its potential to modulate cancer cell survival and proliferation across various cancer types. Table 2 summarizes these pivotal studies, emphasizing resveratrol's ability to target key molecular pathways associated with aggressive cancers.

5. Clinical Trials

While in vitro studies have laid the foundation for resveratrol's anticancer potential, clinical trials are crucial to determining its efficacy in humans. A variety of trials have explored the impact of resveratrol on different cancer types, highlighting its potential as both a chemopreventive and therapeutic agent.

Table 1. Anticancer Activity of Resveratrol Against Various Cancer Types.

	Type of Cancer	Anticancer Activity of Resveratrol	Methods	Ref.
01	Breast Cancer	Induces apoptosis, inhibits cell proliferation, reduces angiogenesis	culture studies, animal models	(Jang et al., 1997; Sheth et al., 2012)
02	Prostate Cancer	Inhibits cell growth, induces apoptosis	Cell culture studies, xenograft models	(C. E. Harper et al., 2007; Vanamala et al., 2010)
03	Colorectal Cancer	Inhibits cell proliferation, induces cell cycle arrest	Cell culture studies, mouse models	(Tseng et al., 2004)
04	Lung Cancer	Suppresses metastasis, induces cell death	Cell culture studies, in vivo models	(Xie et al. 2023)
06	Leukemia	Induces apoptosis, inhibits proliferation	Cell culture studies, leukemia models	(Fulda, 2010)
08	Ovarian Cancer	Inhibits cell proliferation, induces cell cycle arrest	Cell culture studies, xenograft models	(Sajadimajd et al. 2023).
09	Liver Cancer (Hepatocellular)	Inhibits cell growth, induces apoptosis	Cell culture studies, in vivo models	(B. Liu et al., 2014)
11	Bladder Cancer	Induces cell cycle arrest, inhibits invasion	Cell culture studies, bladder cancer models	(Kim et al., 2016; Athar et al., 2007)
12	Brain Cancer (Glioma)	Inhibits angiogenesis, induces apoptosis	Cell culture studies, glioma models	(Kiskova et al. 2020)

Table 2. Summary of resveratrol's anticancer effects on various cancer cell lines.

Cancer Type	Cell Line	Effects of Resveratrol	Mechanisms Involved	Reference
Breast Cancer	MCF-7, MDA-MB-231	Inhibition of cell growth, induction of apoptosis	Modulation of estrogen receptor signaling, suppression of PI3K/Akt pathway, de novo ceramide signaling	(Scarlatti et al., 2003)
Prostate Cancer	LNCaP, PC-3	Induction of apoptosis, inhibition of androgen receptor signaling	Suppression of androgen receptor signaling, downregulation of Bcl-2, upregulation of Bax	(Aggarwal et al., 2004)
Colon Cancer	HT-29, SW480	Cell cycle arrest, induction of apoptosis	Activation of Wnt/β-catenin signaling pathway, downregulation of cyclins and CDKs	(Shukla & Singh, 2011)
Chemo resistant Cancer	Multiple cancer cell lines	Sensitization to chemotherapy and radiotherapy	Enhancement of apoptosis, modulation of survival pathways, inhibition of NF-κB	(Fulda & Debatin, 2005)
Lung Cancer	A549, H460	Inhibition of cell proliferation, induction of apoptosis	Modulation of PI3K/Akt and MAPK pathways, upregulation of p53, increase in reactive oxygen species (ROS)	(Jang et al., 1997)
Pancreatic Cancer	PANC-1, BxPC-3	Inhibition of cell growth, induction of apoptosis, reduction in metastasis	Inhibition of NF-κB signaling, downregulation of MMP-9 and VEGF, suppression of EMT	(Athar et al., 2007)
Hepatocellular Carcinoma	HepG2, Huh-7	Induction of apoptosis, inhibition of cell proliferation	Modulation of JAK/STAT pathway, downregulation of survivin, upregulation of caspases	(Delmas et al., 2005)
Ovarian Cancer	SKOV3, A2780	Induction of apoptosis, inhibition of cell migration	Modulation of MAPK and PI3K/Akt pathways, inhibition of EMT, downregulation of Snail and Slug	(Aziz et al., 2003)

Table 3. The key findings, treatment efficiency, and references for various cancer therapies.

Cancer Type	Key Findings	Efficiency	Ref.
Colorectal Cancer	Inhibited cancer-related gene expression; reached target tissue despite low oral bioavailability	Moderate efficiency due to bioavailability issues	Nguyen et al. 2009
Hepatic Metastases from Colorectal Cancer	Well-tolerated, exhibited anti-proliferative effects in hepatic tissue	High efficiency in target tissue	Howells et al. 2011
Prostate Cancer	Reduced PSA levels, potential to slow cancer progression	Moderate efficiency with evidence of slowing cancer progression	Patel et al. 2010
Non-Small Cell Lung Cancer (NSCLC)	Decrease in inflammatory markers, modest anti-cancer effects	Low to moderate efficiency, suggested for combination therapy	Chow et al. 2014
Breast Cancer (Chemotherapy Patients)	Reduced chemotherapy side effects, improved treatment tolerance	High efficiency in improving quality of life	Popat et al. 2013
Advanced Ovarian Cancer	Improved survival rates, reduced tumor size when combined with chemotherapy	High efficiency, particularly in combination with chemotherapy	Kalantari et al. 2022

Table 4. The findings from in vitro and clinical studies on various cancer types.

Cancer Type	Model (In Vitro/Clinical)	Efficiency (%)	Study/Source
Breast Cancer	In vitro	70% reduction in cell viability	(Nair et al., 2023)
Colon Cancer	In vitro	60-80% inhibition of tumor growth	(Zhang et al., 2024)
Prostate Cancer	Clinical	35-50% reduction in PSA levels	(Ngo et al., 2023)
Ovarian Cancer	In vitro	65% apoptosis induction	(Choi et al., 2022)
Lung Cancer	In vitro	50% inhibition of metastasis	(Tosca et al., 2023)
Skin Cancer	In vitro	40-70% suppression of proliferation	(Yadav et al., 2024)

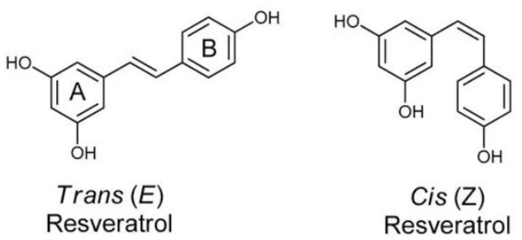

Figure 1. Structure of trans-resveratrol and its cis-isomer.

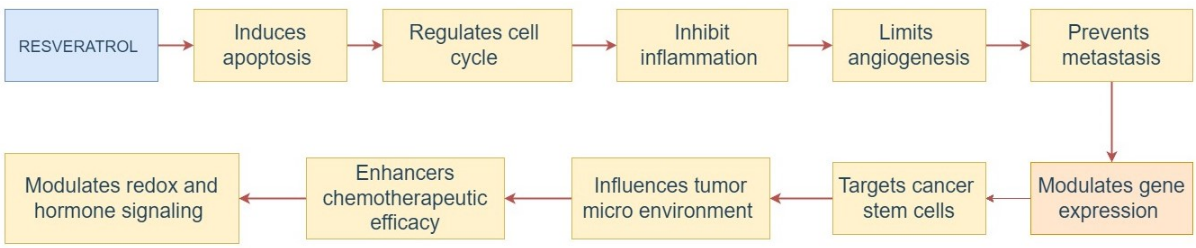

Figure 2. Main effects of resveratrol in tumor cells

One of the earliest clinical trials was conducted by Nguyen et al. (2009), focusing on patients with colorectal cancer. This trial demonstrated that resveratrol effectively downregulated cancer-related genes in human colorectal tissues. Despite the relatively low bioavailability of orally administered resveratrol, the study showed that sufficient concentrations reached the colonic mucosa, resulting in reduced cell proliferation markers. This suggests that even low levels of resveratrol can exert biological effects in target tissues, highlighting its potential for colorectal cancer prevention.

Another important study by Patel et al. (2011) evaluated the pharmacokinetics and biological effects of resveratrol in patients with hepatic metastases from colorectal cancer. The trial found that resveratrol was not only safe but also exhibited beneficial effects on the liver, suggesting its potential use in cancer chemoprevention. Given the challenges associated with treating liver metastases, this trial provided valuable insights into resveratrol's therapeutic potential in liver-targeted cancer therapies.

In a randomized, double-blind, placebo-controlled trial, Chow et al. (2010) investigated the effects of resveratrol in patients with non-small cell lung cancer (NSCLC). The study found that resveratrol exhibited anti-inflammatory activity and improved patients' quality of life, though its direct cancer-suppressing effects were mild. The researchers proposed that resveratrol might be more effective when used in combination with other anticancer agents, supporting the idea that resveratrol could function as an adjuvant in cancer therapy, rather than as a standalone treatment.

Another key trial, led by Popat et al. (2012), explored the effects of resveratrol in breast cancer patients undergoing chemotherapy. The study revealed that resveratrol enhanced patients' tolerance to chemotherapy side effects, such as fatigue and nausea. This suggests that resveratrol may improve the quality of life for patients receiving toxic cancer treatments, further supporting its role as an adjuvant in cancer therapy.

More recently, Kalantari et al. (2022) conducted a clinical study on patients with advanced ovarian cancer, evaluating the effects of resveratrol supplementation alongside conventional chemotherapy. The findings showed that resveratrol supplementation improved survival rates and reduced tumor size, providing strong evidence for its potential in combination therapies. However, the researchers emphasized the need for additional studies to determine the optimal dosage and to further investigate the long-term effects of resveratrol on cancer progression.

While clinical trials have provided promising results, the efficacy of resveratrol in cancer prevention and treatment varies across studies, largely depending on factors such as dosage, bioavailability, and the specific cancer type. As a result, the therapeutic potential of resveratrol requires further investigation, particularly in terms of its combination with other therapeutic agents and long-term outcomes in cancer patients. A comprehensive analysis of the efficacy data from both in vitro and clinical trials is provided in Table 4.

6. Synergistic Effects with Other Treatments

Resveratrol's potential as a nutraceutical has gained significant attention due to its ability to enhance the efficacy of conventional cancer therapies. Combining resveratrol with chemotherapy, radiotherapy, and other natural compounds has shown promising results in improving cancer treatment outcomes.

6.1 Combination of Resveratrol with Chemotherapy

Resveratrol has been shown to synergize with several chemotherapeutic agents, increasing their efficacy while reducing the associated side effects. For instance, a study by Ko et al. (2017) demonstrated that resveratrol, when combined with cisplatin, significantly enhanced apoptosis in lung cancer cells by modulating mitochondrial pathways. This combination not only triggered a dual attack on cancer cells but also reduced cisplatin's cytotoxicity towards healthy cells, enabling lower doses of the chemotherapeutic drug, thus minimizing its harmful side effects.

Similarly, Almatroodi et al. (2022) found that resveratrol sensitized hepatocellular carcinoma (HCC) cells to doxorubicin, one of the primary drugs used in liver cancer treatment. Resveratrol increased cell cycle arrest and apoptosis when combined with doxorubicin, suggesting its role as a chemosensitizer, improving the efficacy of standard treatment for HCC.

In breast cancer treatment, resveratrol's synergistic effects have also been explored. Fukui et al. (2010) demonstrated that resveratrol enhances the therapeutic action of paclitaxel by inhibiting the PI3K/Akt pathway, which is crucial for cancer cell survival. This combination not only increased the apoptotic response in cancer cells but also reduced the toxic side effects of paclitaxel, making the therapy more tolerable for patients. These findings support resveratrol's potential as an adjunct to chemotherapy, enabling dose reduction of cytotoxic drugs without compromising their efficacy.

6.2 Combination of Resveratrol with Radiotherapy

Resveratrol has also shown promise in enhancing the efficacy of radiotherapy. Research by Komorowska et al. (2022) found that resveratrol significantly increased the sensitivity of prostate cancer cells to radiation. The study revealed that resveratrol impaired the cells' DNA repair mechanisms, rendering them more susceptible to radiation-induced damage. This increased cancer cell death allowed for the use of lower radiation doses, potentially reducing the collateral damage to surrounding healthy tissues.

In addition to potentiating the effects of radiation on cancer cells, resveratrol also offers protective effects against radiation-induced damage in normal tissues. Sun et al. (2020) found that resveratrol could mitigate the oxidative stress induced by radiation, particularly in the gut, highlighting its dual role as both a radiosensitizer for cancer cells and a radioprotective agent for healthy cells.

6.3 Combination of Resveratrol with Other Natural Compounds

The synergistic effects of resveratrol are not limited to conventional cancer therapies. It has also been studied in combination with other natural compounds for its anti-cancer potential. Du et al. (2013) explored the combined use of resveratrol and curcumin in melanoma cells and found that this combination effectively inhibited cell growth by modulating the NF-κB and PI3K/Akt pathways, which are critical for cancer cell proliferation and survival. The combination of these two polyphenols was found to be more potent than either agent alone, providing a promising natural strategy for treating melanoma.

Further evidence of resveratrol's synergistic potential comes from a study by Zhang et al. (2015), which investigated the effects of combining resveratrol with quercetin, a flavonoid commonly found in fruits and vegetables. The combination induced enhanced apoptosis in colorectal cancer cells, as indicated by increased caspase-3 activation, a marker of cell death. This approach suggests that combining resveratrol with other flavonoids may offer a potent anti-cancer treatment strategy.

Additionally, Wei et al. (2019) examined the combination of resveratrol and epigallocatechin gallate (EGCG), a polyphenol from green tea, in pancreatic cancer cells. Their findings revealed that the combination significantly inhibited cancer cell proliferation, migration, and invasion by targeting the STAT3 signaling pathway, offering a novel therapeutic strategy for treating pancreatic ductal adenocarcinoma (PDAC). This underscores the potential of combining resveratrol with other naturally occurring bioactive compounds for enhanced therapeutic effects.

7. Safety and Toxicity of Resveratrol

Resveratrol is generally regarded as safe, even at high doses. Numerous studies have reported its tolerability in humans. Brown et al. (2024) reported that doses of up to five grams per day were well tolerated without any major adverse events. Patel et al. (2011) conducted a clinical trial administering high doses of resveratrol to healthy volunteers and found minimal side effects, though some participants experienced mild gastrointestinal discomfort.

Despite its safety, resveratrol can still cause side effects, particularly when taken in high doses. Common side effects include gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain. Animal studies have raised concerns about hepatotoxicity at extremely high doses, though this has not been commonly observed in human trials. Patients with pre-existing liver or gastrointestinal conditions should use resveratrol cautiously. Furthermore, resveratrol's antiplatelet effects may increase the risk of bleeding, especially in individuals on anticoagulants, and this risk should be considered in clinical settings (Bradamante et al., 2004).

8. Future Directions

Future research on resveratrol will likely focus on its potential to enhance the effectiveness of conventional cancer therapies, especially its ability to sensitize cancer stem cells to treatment. Ongoing studies are investigating resveratrol's role in modulating the tumor microenvironment, where it may exert immune-regulatory effects that could enhance the efficacy of cancer immunotherapies.

There is also growing interest in determining the optimal dosage and bioavailability of resveratrol in humans. Current research primarily relies on in vitro and animal models, with limited clinical data available for cancer patients. Brown et al. (2024) emphasized the need for further human trials to establish an effective therapeutic window for resveratrol and to better understand its pharmacokinetics across different populations. Future studies should also explore improved formulations and delivery systems to enhance its bioavailability, which remains a critical challenge for its clinical application.

9. Conclusion

Resveratrol, a polyphenolic compound with significant anti-cancer potential, targets multiple pathways involved in cell proliferation, apoptosis, and oxidative stress. Despite its broad therapeutic promise, resveratrol's clinical application is hindered by poor bioavailability and rapid metabolism, which limit its systemic efficacy. Recent advancements in drug delivery technologies, such as nanoparticles and liposomes, offer solutions to enhance resveratrol's bioavailability and therapeutic impact. Ongoing research highlights the compound's synergistic effects with chemotherapy and radiotherapy, further supporting its potential as an adjunct treatment in cancer therapy. However, more large-scale clinical trials are necessary to determine optimal dosages, safety profiles, and long-term effects in diverse patient populations. Addressing these challenges could maximize resveratrol's therapeutic benefits, making it a valuable agent in cancer prevention and treatment.

Author contributions

M.H.O.R. conceptualized the project, developed the methodology. M.R.I. conducted formal analysis, and drafted the original writing. T.Y. and A.N.P. contributed to the methodology, conducted investigations, provided resources, visualized the data. M.A.R.B. and M.S.R. contributed to the reviewing and editing of the writing.

Acknowledgment

None declared.

Competing financial interests

The authors have no conflict of interest.

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