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Review Article

Therapeutic benefits and limitations of resveratrol in cancer: A comprehensive review

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Abstract

Resveratrol, a natural phenolic compound with antiproliferative characteristics, is under investigation for its potential in several biological functions. It is present in red wine, peanuts, blueberries, raspberries, and grape skins. Researchers employ keywords and phrases to locate open-access articles. Diverse keywords and phrases have been used to search for open-access publications in Google Scholar, DOAJ, Scopus, and other free databases. Boolean operators were utilized to filter and sort the highest-quality recent articles. Resveratrol, a small polyphenol, has potential as a therapy and preventive agent for various diseases. It has anti-aging, anti-carcinogenic, anti-inflammatory, and antioxidant properties and has protective effects on different cancers. It inhibits tumor cell growth, promotes immune responses, and prevents cell adhesion. In India, incorporating resveratrol into diets is essential because it can boost immunity, antioxidants, and health benefits, especially in vegetarian and vegan diets.

Keywords: Resveratrol, Anticarcinogenic, Antioxidants, Cancers, Leukemia, Malignancies

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1. Introduction

Resveratrol, a natural phenol with a C6–C2–C6 structure, is gaining research due to its pharmacological potential. Resveratrol has antiproliferative properties in red wine, peanuts, blueberries, raspberries, and grape skin. Its biological activities include anti-inflammatory, vasorelaxant, anticancer, oestrogenic, lipid metabolism-modulating, copper chelation, free radical scavenging, eicosanoid synthesis modification, lipid peroxidation inhibition, and antibacterial, antifungal, and antivirus properties.[1,2]

2. Methods

Various keywords and phrases have been used to search open-access articles in Google Scholar, DOAJ, Scopus, and other free databases. Some boolean keywords were used for filtering and sorting the best quality latest articles.

3. Discussion

3.1. Pharmacological benefits of resveratrol

3.1.1. Antioxidant and anti-inflammatory effects

Studies show resveratrol's potent antioxidant activity, scavenging radicals like superoxide and hydroxyl radicals and activating antioxidant enzymes. Its protective effect against oxidative stress is demonstrated by increased intracellular reduced glutathione and membrane sulfhydryl groups. So, it is one of the best antioxidants to prevent cancer.[1,3]

3.1.2. Cardioprotective effect

Epidemiological studies suggest that resveratrol contributes to the "French Paradox," indicating that moderate wine consumption reduces cardiovascular disease risk. This is due to its antiproliferative, antioxidant, and anti-inflammatory properties and ability to modulate cell signaling pathways and regulate vascular homeostasis. In animal research,

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resveratrol was found to have a more substantial protective effect against ischemia-reperfusion-induced arrhythmias and mortality.[1]

3.1.3. Neuroprotective effects

Resveratrol exhibits potential in neurodegenerative conditions such as Parkinson's and Alzheimer's by reducing oxidative stress, regulating amyloid-beta aggregation, and stimulating sirtuins. Most cancer patients often face neuro-degenerative diseases. So, resveratrol would be one of the best preventive therapeutic agents.[5]

3.1.4. Anticancer properties

Resveratrol, a natural molecule, exhibits anticancer characteristics by inhibiting the proliferation of diverse tumor cell types, particularly those linked to lymphoid and myeloid malignancies. Resveratrol inhibits the multistep process of carcinogenesis at several stages, according to in vivo studies. It reduces tumor start, development, and progression and prevents carcinogen activation by blocking aryl hydrocarbon-induced CYP1A1 production and activity. Resveratrol has anti-cancer therapeutic properties in addition to chemopreventive ones.[6]

3.1.5. Bioavailability

A paper discusses the absorption, bioavailability, and metabolism of resveratrol in humans, focusing on humans. Oral absorption is 75%, mainly through transepithelial diffusion. Bioavailability is less than 1%, and dose escalation doesn't significantly alter this. Primary metabolites include glucuronides and sulfates, but reduced dihydro resveratrol conjugates may account for up to 50% of an oral dose.[7]

Resveratrol, a small polyphenol, has been studied for potential therapies and preventive agents for various diseases. It has anti-aging, anti-carcinogenic, anti-inflammatory, and anti-oxidant properties. However, few human studies have explored its physiological effects. Despite numerous clinical trials, resveratrol's safety and bioavailability remain unclear. This review aims to examine the current knowledge on resveratrol's effects on humans and develop guidelines for human clinical trials.[8] Resveratrol has been shown to have protective effects on various cancers, including colorectal, lung, breast, prostate, ovarian, cervical, liver, and gastric cancer.

3.2. Roles of resveratrol in various cancers

3.2.1. Colorectal cancer

The substance inhibits colorectal cancer growth by downregulating Kirsten rat sarcoma virus expression, prevents lung cancer tumorigenesis by glycolysis process, and promotes apoptosis and antiproliferative effects in LNCaP cells.

However, lower doses have improved efficacy in colorectal cancer chemoprevention and AMP-activated protein kinase upregulation.[9]

3.2.2. Ovarian cancer

This cancer type reduces ovarian cancer cell adhesion to increase soluble hyaluronic acid. An ideal chemo-preventive agent should target biochemical and physiological pathways supporting tumor development, modulating standard growth control to preneoplastic or cancerous cells, with minimal toxicity against healthy tissues. Resveratrol, a type of polyphenol, has antioxidant and anti-inflammatory properties, possibly mediated by DNA methylation and histone modification. With its strong anticancer properties and minimal toxicity in animal models, Resveratrol has been used in human studies by the National Cancer Institute for cancer prevention in healthy volunteers, suggesting its potential as a complementary medicine adjunct.[10]

3.2.3. Gastric cancer

Resveratrol effectively prevents the invasion and migration of human gastric cancer cells by preventing the epithelial-to-mesenchymal transition. Gastric cancer is linked to lifestyle factors, including diet and H. pylori infection. Polyphenolic compounds like resveratrol have antioxidant and anti-inflammatory properties, making them a potential candidate for GC prevention and therapy. Sustained resveratrol levels can have a powerful antitumoral effect, and finely modulated administration can activate anti-cancer mechanisms.[11]

3.2.4. Breast cancer

Resveratrol has been found to inhibit breast cancer proliferation at high concentrations, while low concentrations increase it. It also increases estrogen precursor steroids and inhibits active steroid inactivation, leading to cancer cell growth. Resveratrol exhibits anticancer properties by inhibiting cancer cell growth, promoting immune responses, and preventing cell adhesion while impairing glycolysis. Cancer metastasis requires regulatory immune cells like Foxp3+CD4+ Tregs (regulatory T cells) and TGF-β-expressing tBregs (Tumor-evoked regulatory B cells). Breast cancer produces metabolites that induce tBreg generation, which protects cancer cells by inactivating NK cells and downregulating effector CD8+ T cells. Low and noncytotoxic doses of resveratrol can inhibit breast cancer progression and lung metastasis by inactivating tBregs. Resveratrol does not affect MDSCs (Myeloid-derived suppressor cells) but promotes 4T1 cancer escape and expands Tregs.[12]

Table 1: Some critical studies to review the anticarcinogenic effects of resveratrol

Study group	Study type	Interventions	Key observation	References
The sample size totals 2618 of the Iranian population mixed with males and females.	Cross-sectional study	The dose of 0.48 mg/day to 5.75 mg/day was applied to the food frequency questionnaire for one year.	The study found a high vitamin C intake, particularly 0.054 mg/day, in the case of HTN.	[14]
The sample size totals 971 of the Swiss population mixed with males and females.	Cross-sectional study	The food-frequency questionnaire (FFQ) reveals three tertiles: T1 (0-74.0 µg/day), T2 (73.0-161.0 µg/day), and T3 (>161. µg/day) two years prior.	The study found that certain factors, such as age, gender, and education, were found to be inversely associated with a higher risk of breast cancer.	[15]
The sample size totals 1400 of the Swiss population mixed with males and females.	Cross-sectional study	The dosage of FFQ (20 years prior) was adjusted to 0.09 mg/day, with the control being 0.1 mg/day.	The study found a significant negative relationship between the risk of three subtypes of esophageal cancers.	[16]
The sample size totals 39 males.	Double-blind Randomised Control Trial	Resveratrol 10-100 mg/day for 12 weeks	The study found a decrease in methylation ($p = 0.047$), while the null group did not change significantly prostaglandin E2.	[17]

3.3. Indian diet types

The inclusion of resveratrol in the diet is essential and considerable. Western diet patterns have already been incorporated in many ways through different foods. Polyphenols like Naringin, hesperidin, flavanones, and anthocyanins boost immunity, antioxidants, and health benefits. Vegetarian, non-vegetarian, and Mediterranean diets are popular worldwide. In India, many people are vegetarian or vegan, with vegetarians in the north and west and Jains typically vegan. However, a considerable amount of RSV can be added with the help of dietitians' guidelines for better anticarcinogenic effects.[13]

The Indian diet, rich in spices, citrus fruits, vegetables, herbal tea, and honey, has strengthened the immune system, highlighting the importance of diet and Ayurveda research in the West.[18] Resveratrol is another significant addition to the list of Indian foods.

3.4. Limitation in clinical application

The following reasons restrict resveratrol's therapeutic application despite favorable preclinical results:

1. Poor Bioavailability: The primary cause of resveratrol's diminished actions in living things is its poor bioavailability. The substance's extensive metabolism is most likely the cause of this. Resveratrol's systemic availability is decreased by its quick metabolism, mainly transforming it into glucuronide and sulfate conjugates.[7]
2. Poor solubility in water: One of the factors contributing to resveratrol's limited bioavailability is its solubility in water, which is 0.05 mg/mL. In biological systems, the hydrophobic nature restricts dispersion and absorption.[8]
3. Low Stability: Resveratrol also tends to be unstable in several situations. Research shows that while resveratrol is stable in neutral and acidic conditions, it breaks down quickly at higher pH values and temperatures.[1,8]

4. Conclusion

Resveratrol is a promising medicinal agent due to its extensive health benefits, including antioxidant, anti-inflammatory, cardioprotective, and anticancer properties. However, its clinical application is still tricky because of its poor pharmacokinetics and low bioavailability, drastically diminishing its therapeutic efficiency in different types of cancer. Future studies should improve the medication's solubility, stability, and bioavailability to get around these restrictions. Additionally, prodrug tactics and structural changes may enhance its metabolic profile and prolong its half-life, guaranteeing more reliable therapeutic results. The entire therapeutic potential of resveratrol in cancer can be achieved by resolving these pharmacokinetic issues, opening the door to more or more effective clinical applications.

5. Source of Funding

None

6. Conflict of interest

None

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