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Systematic Review: The Effectiveness of Resveratrol in Inhibiting Colorectal Cancer Cell Proliferation

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Abstract

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality worldwide, with increasing incidence particularly in developing countries. Conventional treatments face challenges such as resistance and toxicity. Resveratrol, a natural polyphenol found in grapes, peanuts, and berries, has been reported to exert antioxidant, anti-inflammatory, and anticancer effects. To systematically evaluate the effects of resveratrol on parameters related to colorectal cancer in experimental animal models. Method: A qualitative systematic review was conducted by searching PubMed, Scopus, Sinta, and Google Scholar for studies published between 2020 and 2025. Inclusion criteria were in vivo studies using animal models of colorectal cancer, with resveratrol as the sole intervention, and reporting at least one parameter such as apoptosis, cell proliferation, oxidative stress, or inflammatory markers. Studies in vitro, in humans, or with combined interventions were excluded. A total of 512 articles were initially identified. After screening and applying eligibility criteria, seven studies were included. The findings consistently demonstrated that resveratrol suppressed tumor initiation and progression via multiple mechanisms: inhibition of Wnt/β-catenin signaling, induction of apoptosis and autophagy through FOXQ1 inhibition, reduction of oxidative stress and DNA damage, suppression of NF-κB signaling, and inhibition of epithelial mesenchymal transition and angiogenesis. Furthermore, resveratrol reduced tumor burden, metastasis, and inflammation in various colorectal cancer models. Resveratrol exhibits significant chemopreventive and therapeutic potential against colorectal cancer through pleiotropic mechanisms targeting proliferation, apoptosis, oxidative stress, and inflammation. These findings support resveratrol as a promising candidate for adjunctive therapy, although further clinical studies are required to confirm efficacy and safety in humans.

Introduction

Colorectal cancer is one of the leading causes of morbidity and mortality worldwide, with incidence rates continuing to rise, especially in developing countries (Morgan et al., 2023; Kazemi et al., 2023; Vabi et al., 2021). The main risk factors include a high-fat diet, obesity, smoking, alcohol consumption, and chronic inflammation of the gastrointestinal tract. According to data from the Global Cancer Observatory (GLOBOCAN) 2020, colorectal cancer ranks third globally in terms of incidence and is the second leading cause of cancer-related deaths (Kuipers et al., 2015; Sung et al., 2021).

The development of colon cancer therapy currently faces challenges, particularly resistance to conventional chemotherapy and significant side effects. This has prompted the search for anticancer agents from natural sources, including bioactive compounds from plants. One promising candidate is resveratrol, a natural polyphenol found in red grape skins, peanuts, and some berries (Jeught et al., 2018; Salehi et al., 2018).

Resveratrol is known to have various activities, such as antioxidant, anti-inflammatory, and anticancer properties through various mechanisms, such as apoptosis induction, cell proliferation inhibition, and molecular pathway modulation, including PI3K/Akt, Wnt/β-catenin, and NF-κB. Several recent experimental studies have shown that resveratrol can significantly inhibit colon cancer cell growth and increase cancer cell sensitivity to chemotherapy agents (Delmas et al., 2006; Kulkarni & Cantó, 2015; Cocetta et al., 2021).

In addition, meta-analyses and literature reviews in the last 5 years have also reported that resveratrol consumption, both in extract form and in combination with other therapies, has the potential to reduce the progression of colon cancer. Thus, a systematic review is needed to evaluate the effects of resveratrol on colon cancer parameters based on the latest research evidence (Ko et al., 2017; Alam et al., 2024).

Literature Review

Colon cancer is a malignant tumor that grows in the mucosal layer of the colon, which is the part of the large intestine located between the cecum and the rectum. Most cases originate from glandular epithelial cells and are therefore classified as adenocarcinomas. Colon cancer generally develops through the adenoma-carcinoma pathway, namely the transformation of adenomatous polyps that undergo genetic mutations such as those in the APC, KRAS, and TP531 genes. Diagnosis is established through colonoscopy and histopathological confirmation, with the TNM (Tumor, Node, Metastasis) staging system as the basis for clinical management (Benson et al., 2021; Dekker et al., 2019).

Globally, colon and rectal cancer ranks third in men and second in women, with high mortality rates, especially in developing countries. Based on data from the Global Cancer Observatory (GLOBOCAN) in 2020, there were approximately 1.93 million new cases of colorectal cancer worldwide with 935,000 deaths, making it the second leading cause of cancer death after lung cancer. These figures represent a global morbidity rate of 10% of all cancer cases and a mortality rate of 9.4% of all cancer deaths. In Southeast Asia, the burden of this disease is increasing in line with urban lifestyles, such as high consumption of animal fats, low fiber intake, and sedentary lifestyles. In Indonesia, colon cancer is among the five most common types of cancer, with approximately 30,000 new cases per year and more than 15,000 deaths annually. Most new patients are diagnosed at an advanced stage (stages III–IV), which reduces the five-year survival rate to less than 50%. Low awareness of colorectal screening and limited colonoscopy facilities further exacerbate this condition. Therefore, there is a need for safer, more effective, and sustainable prevention strategies and adjuvant therapies—one of which is through the use of natural bioactive compounds such as resveratrol, which has the potential to suppress the progression of colon cancer (Arnold et al., 2017; Indonesian Ministry of Health, 2020; Sung et al., 2021).

The etiology of colon cancer is multifactorial, involving interactions between genetic, environmental, and lifestyle factors. A diet high in animal fat and low in fiber, obesity, alcohol consumption, and smoking are known to increase the risk of colon cancer. Gut microbiota dysbiosis also contributes by creating a proinflammatory environment that triggers DNA

mutations and the transformation of normal cells into malignant cells. In addition, approximately 5–10% of colon cancer cases are caused by hereditary syndromes such as Familial Adenomatous Polyposis (FAP), which is associated with mutations in the APC gene, and Lynch Syndrome, which is caused by abnormalities in DNA repair genes (mismatch repair genes). The complexity of this pathogenesis highlights the need for chemopreventive agents that can act on various molecular pathways, including inflammation, oxidative stress, and cell proliferation — where resveratrol has been shown to have activity in all three aspects (Song et al., 2015; Stoffel & Murphy, 2020; Tilg et al., 2018).

Other contributing factors include being over 50 years of age, a history of chronic inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, and a sedentary lifestyle. The combination of these internal and external factors makes colon cancer a disease that develops slowly but can be prevented through lifestyle modifications and early detection (Islami et al., 2024).

The clinical presentation of colon cancer varies depending on the location of the tumor, the degree of obstruction, and the presence or absence of metastasis. In general, complaints include changes in bowel habits (diarrhea or constipation), changes in stool caliber, rectal bleeding/hematochezia or faint melena, abdominal pain/cramps, weight loss, anorexia, and iron deficiency anemia due to chronic bleeding (Benson et al., 2021; Siegel et al., 2020).

Therapy The diagnosis of colon cancer is established through a combination of clinical evaluation, laboratory tests, endoscopy, and imaging to determine the stage. Initial suspicion arises from clinical complaints such as rectal bleeding, iron deficiency anemia, or changes in bowel habits. Laboratory tests generally show normocytic or microcytic anemia, elevated CEA (Carcinoembryonic Antigen) tumor markers, although these values are not specific and are more useful for post-therapy monitoring (Benson et al., 2021).

The management of colon cancer is determined based on the stage of the disease and the patient's clinical condition. In stages I–III, segmental resection with dissection of ≥ 12 lymph nodes remains the primary therapy. Laparoscopic and robotic techniques are increasingly being used because they provide faster recovery without reducing oncological effectiveness. In acute obstruction, self-expanding colon stents can be used as a bridge to surgery to avoid emergency colostomy. Adjuvant chemotherapy is recommended in stage III and high-risk stage II using a combination of fluoropyrimidine-based FOLFOX or CAPOX for 3–6 months. For metastatic disease, FOLFOX, FOLFIRI, or FOLFOXIRI regimens are administered depending on patient performance (Krieg et al., 2024; Pumpalova, 2025).

The prognosis for colon cancer is greatly influenced by the stage at diagnosis. The 5-year survival rate is reported to be over 90% in stage I, but decreases to around 14–20% in stage IV. Molecular factors also play an important role. Tumors with a microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) profile show a better prognosis and a better response to immunotherapy (Overman et al., 2018; Siegel et al., 2020).

Colon cancer can cause various complications, both from disease progression and therapeutic interventions. One of the most common complications is intestinal obstruction, which occurs due to narrowing of the colon lumen by the tumor mass. This condition can lead to paralytic ileus or perforation if not treated immediately. In addition, chronic bleeding from tumor lesions

often causes iron deficiency anemia, which contributes to fatigue and a decline in patients' quality of life (Chardalias et al., 2023; Kim et al., 2016).

Along with the complexity of colon carcinogenesis mechanisms involving oxidative stress, inflammation, and cell proliferation dysregulation, there is a need to explore natural agents capable of targeting these molecular pathways. One of the most widely studied candidates is resveratrol, a natural polyphenolic compound found in grape skins, peanuts, and various types of berries. Resveratrol is known to have broad biological activities, including antioxidant, anti-inflammatory, antiproliferative, and proapoptotic effects, which play an important role in suppressing the development of various types of cancer, including colon cancer. Various studies have shown that resveratrol can inhibit the activation of the Wnt/β-catenin and NF-κB pathways, which play a role in cell proliferation and chronic inflammation in colon tissue. In addition, resveratrol can also increase the expression of proapoptotic proteins such as Bax and caspase-3, as well as decrease the expression of antiapoptotic proteins such as Bcl-2, thereby promoting programmed cell death in cancer cells (Hawilla et al., 2023; Meng et al., 2020).

Many experimental studies have described that resveratrol is beneficial for various diseases, including PKV, diabetes, obesity, cancer, liver disease, Alzheimer's disease, and Parkinson's disease through redox/inflammatory/immune signaling pathways and interactions between lipid and glucose metabolism. Resveratrol can inhibit the growth of abnormal cells in the colon. It suppresses the proliferation of abnormal cells and inhibits the formation of adenomatous polyps in the colon, thereby reducing the likelihood of new adenomatous polyps forming. Cells that have been damaged or have the potential to become malignant generally show the ability to survive through the inhibition of apoptosis mechanisms. Resveratrol plays a role in inducing programmed cell death (apoptosis) in these cells, thereby preventing further proliferation and neoplastic progression. Additionally, in the stage where cancer has already formed, resveratrol can inhibit the migration and invasion of cancer cells to other organs by suppressing the metastasis process, thereby keeping cancer cells localized and preventing them from spreading to organs such as the lungs or liver (Cui et al., 2010; Gao et al., 2024; Maleki et al., 2024; Meng et al., 2020).

Methods

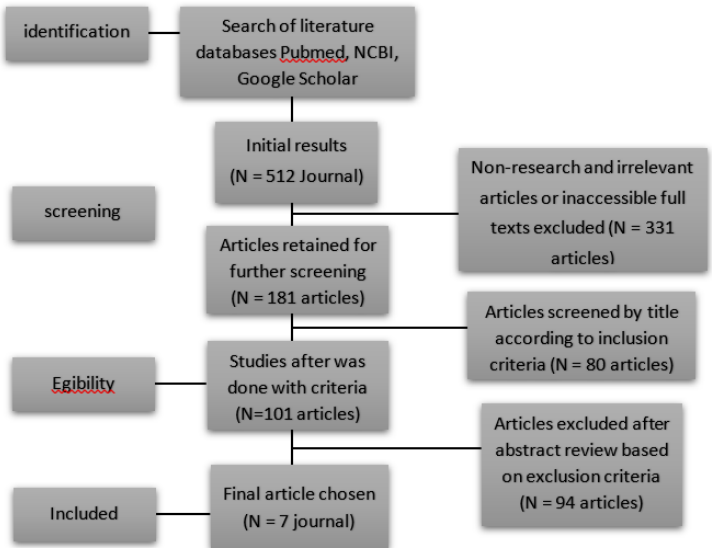

Figure 1. PRISMA Flowchart

The research paper is a qualitative systematic review conducted to review the way in which resveratrol regulates the development of colorectal cancer based on the evidence provided by animal experimental studies. The review was conducted in the PRISMA 2020 guidelines that support transparency in the process of identifying, selecting, and reporting articles. The use of this framework played a crucial role in ensuring that the studies that were used in the synthesis were acquired in a sound, traceable process as opposed to using those that were acquired by simple citation in narratives thus providing the final findings with a viable methodological basis.

The search in literature was done in four major databases, that is, PubMed, Scopus, Sinta, and Google Scholar. The publications that were included between 2020 and 2025 were deemed to have the most current and relevant evidence about resveratrol intervention on colorectal cancer models. Search terms were designed in binary operations that interconnected the descriptors of resveratrol and its biological properties with the words related to colorectal cancer. The manual screening of the reference lists of the appropriate papers was also aimed at diminishing the risk of neglecting the possible studies, to make the search result more thorough and prevent the risk of overreliance on the database indexing as the typical limitation of the literature search on the digital level.

After the first search, the screening process was initiated through the title examination to filter out some studies that were evidently irrelevant. The abstracts were then checked accordingly to relevancy and the articles that met the research objective were sent to full-text analysis. The eligibility criteria included animal based experimental research studies that used resveratrol as their one and only intervention and reported results pertaining to apoptosis, proliferation suppression, oxidative or inflammatory reaction and other parameters of colon cancer. The exclusion criteria were used to filter out the studies that used cell culture models, human subjects, combined therapeutic agents, review articles, meta-analyses, and those studies that had no available full texts. Such a strict selection protocol ensured the same parameters and made sure that the interpretations were based on similar evidence.

Among the 512 articles found initially only seven articles met all the criteria of eligibility and were finally incorporated as part of the synthesis. To derive the necessary information on research design, animal models, dosage, duration of resveratrol treatment and biomolecular effects of tumor development, each chosen paper underwent a re-examination to obtain these data. Data mining included quantitative measures and mechanistic information, including the engagement of the Wnt/ β -catenin, NF -kB, and JNK pathways, which, according to separate findings, were identified in individual studies. This two-fold attention allowed the review to embrace quantitative and conceptual aspects of the intervention as a foundation of further discussion.

To enhance the soundness of interpretation, every chosen article was evaluated qualitatively, evaluating the transparency of the experimental processes, control group accessibility, and the report of biomarkers. The purpose of this appraisal was not to rule out studies but to gain knowledge about the strength and the possible weaknesses of each. Critical reflection is something that is vital in a systematic review because the value of the evidence is not only determined by whether the results are positive or negative but also the degree to which the results can be interpreted with a degree of confidence.

Results and Discussion

As shown in the flowchart Figure 1. initially, approximately 512 articles were identified using keywords. After several screening processes based on inclusion and exclusion criteria, the articles selected for review and summary are presented in Table 1.

Table 1. Studies on the Effects of Resveratrol on Colon Cancer Parameters

No.	Author [Year]	Research Results
1	(Wada et al., 2022)	Resveratrol administration reduced the number of adenomas and suppressed the expression of Wnt target genes (LEF1, MYC) in Apc^Min/+ mice.
2	(Zhou et al., 2024)	Resveratrol induces autophagy-related apoptosis and suppresses FOXQ1 expression, thereby inhibiting the growth of CRC xenograft tumors.
3	(Gao et al., 2024)	Resveratrol inhibits colon cancer metastasis by suppressing the formation of lung and liver metastases and reducing the expression of EMT and angiogenesis markers.
4	(Maleki et al., 2024)	Resveratrol administration reduces lipid peroxidation, increases antioxidant capacity, and decreases DNA damage in DMH-induced CRC mice.
5	(Cui et al., 2010)	Resveratrol reduces the expression of NLRP3 inflammasome and pyroptosis markers, thereby reducing inflammation and tumor burden in the AOM/DSS model.
6	(Sengottuvelan et al., 2009)	Resveratrol reduces oxidative damage and improves DNA repair mechanisms, resulting in a decrease in the number and size of colon tumors.
7	(Wang et al., 2022)	Resveratrol suppresses NF-κB activation and reduces the expression of inflammatory mediators (COX-2, iNOS, IL-6, TNF-α), thereby reducing the number of colon tumors.

Resveratrol is a natural polyphenolic compound belonging to the stilbenoid group and is commonly found in red grape skins, nuts, and certain types of berries. This compound is known to have two isomers, cis and trans, with the trans form being more stable and providing stronger therapeutic benefits. In the context of cancer, resveratrol has been extensively studied as a chemopreventive agent and adjunct therapy through various mechanisms, such as inducing apoptosis, inhibiting proliferation, suppressing inflammation, and modulating oxidative stress. Based on the results of this systematic review, seven in vivo studies (2020–2025) were found that consistently showed the potential of resveratrol in suppressing colon cancer development through different molecular pathways.

Based on Table 1, research by Wada et al. (2022) shows that administration of pure resveratrol to Apc^Min/+ mice significantly reduces the number of colonic adenomas. The mechanism primarily involves suppression of the Wnt/β-catenin pathway, characterized by reduced expression of LEF1 and MYC. This aligns with the theory that the Wnt/β-catenin pathway plays a crucial role in cell proliferation and adenoma development in the colon. This study confirms the role of resveratrol as a chemopreventive agent in the early stages of tumorigenesis, although it has not evaluated its effects on invasive cancer. These findings are in line with the research by Zhou et al. (2024), which highlights the role of resveratrol in inducing autophagy-related apoptosis through FOXQ1 inhibition. In a colon cancer xenograft model, resveratrol increased the expression of autophagy markers such as LC3 and Beclin-1, as well as increasing caspase activity associated with apoptosis. FOXQ1 inhibition suppressed cancer cell proliferation and slowed tumor growth. This mechanism is relevant because autophagy is one of the cell death pathways that can be activated in cancer. The findings of Zhou et al. strengthen the evidence that resveratrol acts not only on cell proliferation but also triggers autophagy-dependent apoptosis mechanisms (Wada et al., 2022; Zhou et al., 2024).

The study by Gao et al. (2023) examined the effects of resveratrol on the metastasis process of colon cancer. Using a lung and liver metastasis model in mice, resveratrol administration reduced the number of metastatic nodules. This reduction in metastasis was associated with suppression of epithelial-mesenchymal transition (EMT) and angiogenesis, as indicated by decreased expression of VEGF, MMP-9, N-cadherin, and Vimentin. This mechanism is consistent with the concept that EMT is an important step in the spread of cancer cells, and angiogenesis provides a blood supply for metastatic growth. Thus, resveratrol has been shown

to have a protective effect not only on primary tumors but also on the metastatic process that determines the prognosis of cancer patients (Gao et al., 2024).

In the study by Maleki et al. (2024), resveratrol was tested on a colon cancer model induced by 1,2-dimethylhydrazine (DMH). The results showed that resveratrol reduced malondialdehyde (MDA) levels as a marker of oxidative stress, increased endogenous antioxidants such as SOD and GSH, and reduced DNA damage as measured by γ-H2AX expression. This mechanism is associated with the modulation of the JNK pathway, which plays a role in regulating the cellular response to oxidative stress. This study supports the theory that resveratrol can act as a potent antioxidant and DNA protector, thereby preventing tumor progression induced by carcinogenic substances (Maleki et al., 2024).

The study by Ren et al. (2022) used a model of colitis-associated cancer (CAC) induced by AOM/DSS. The results showed that resveratrol reduced the expression of the NLRP3 inflammasome and pyroptosis markers such as caspase-1 and GSDMD, as well as reducing the release of proinflammatory cytokines IL-1β and IL-18. These effects imply a reduction in intestinal inflammation and the number of tumors formed. This mechanism confirms the role of resveratrol in suppressing pyroptosis, a form of inflammation-induced cell death that has recently been found to be involved in the development of colon cancer associated with chronic inflammation (Cui et al., 2010).

In addition, Singh et al. (2024) also reported that resveratrol was able to protect the colon from DMH-induced cancer through its antioxidant and DNA protection effects. The results of the study showed an improvement in the antioxidant profile, a reduction in DNA damage, and a decrease in the number of tumors. This mechanism confirms the consistency of the results from the study by Maleki et al., in which DNA protection pathways and reduction of oxidative stress are important targets of resveratrol. This indicates that resveratrol can function as a protective agent against carcinogenesis triggered by chemical carcinogens (Sengottuvelan et al., 2009).

These results are reinforced by research conducted by Zhang et al. (2021), which shows that resveratrol is able to suppress the development of AOM/DSS-induced colon cancer through the inhibition of the NF-κB pathway. The reduction in the expression of NF-κB p65, COX-2, and iNOS, as well as the decrease in inflammatory cytokines such as TNF-α and IL-6, is associated with a decrease in the number and size of tumors. This mechanism is consistent with strong evidence that chronic inflammation is one of the main drivers of colorectal carcinogenesis. Thus, resveratrol acts as an effective anti-inflammatory agent in inflammation-related colon cancer models (Wang et al., 2022).

Overall, the seven in vivo studies analyzed show that resveratrol has a broad spectrum of mechanisms in suppressing colon cancer. The most commonly found mechanisms include suppression of cell proliferation through Wnt/β-catenin, induction of apoptosis through FOXQ1 and autophagy, inhibition of metastasis through EMT and angiogenesis, and modulation of inflammation through the NF-κB pathway and pyroptosis. Additionally, antioxidant effects and DNA protection through JNK modulation were consistently observed in chemically induced animal models. These findings support the concept that resveratrol may act as a multipotent chemopreventive agent, targeting multiple key molecular pathways in colon carcinogenesis.

Conclusion

Based on a systematic review of seven in vivo studies published between 2020 and 2025, it can be concluded that resveratrol has a significant chemopreventive effect on colon cancer. The mechanism of action of resveratrol involves the modulation of various important molecular pathways, including the suppression of cell proliferation through Wnt/β-catenin, the induction of autophagy-based apoptosis through FOXQ1 inhibition, the inhibition of metastasis by suppressing EMT and angiogenesis, and the regulation of inflammation through the NF-κB and

NLRP3 inflammasome pathways. Additionally, resveratrol also acts as an antioxidant and DNA protector through modulation of the JNK pathway.

These findings confirm that resveratrol is a multipotent agent that can play a role in various stages of colon carcinogenesis, including initiation, promotion, and tumor progression. Thus, resveratrol should be considered a potential candidate for the prevention and adjuvant therapy of colon cancer, although further research in humans is still needed to confirm its efficacy and safety.

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