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Cytotoxic and Cytostatic Activity of Resveratrol: An Updated Scoping Review

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ABSTRACT— Cancer remains one of the leading causes of mortality among non-communicable diseases worldwide, underscoring the need for extensive searches for effective treatments and therapeutic agents. Resveratrol, a naturally occurring polyphenol, has been the subject of interest in many cancer studies for its anti-cancer potential and is continuously being studied to this date. This scoping review aimed to provide an updated synthesis of the cytotoxic and cytostatic activity of resveratrol, focusing on in vitro and in vivo studies published from 2019 to 2024. Using PRISMA-ScR guidelines, this review has identified the molecular mechanisms of resveratrol, including apoptosis induction, modulation of autophagy, and inhibition of proliferative pathways. The key findings of this study contribute to the supporting evidence of resveratrol's anticancer potential, emphasizing the further need for clinical trials to validate its therapeutic effects.

KEYWORDS: Cancer, Cytostatic, Cytotoxic, In vitro, In vivo, Resveratrol.

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1. Introduction

Cancer remains to be the leading cause of death under non-communicable diseases worldwide that afflict the well-being of an individual [1]. This disease is known to have the characteristic of uncontrolled proliferation of cells disrupting the physiological mechanisms in cellular level [2]. The human body rules out any diseases on its own by several processes that require the function of the innate and adaptive immune system. However, cancer cells act differently by hiding themselves from immune responses by secreting cytokines, impeding antigen recognition, exhausting T cells, and inhibiting the immune system [3]. The mechanism of cancer cells recruits regulatory T cells to suppress Natural killer cells and cytotoxic T cells from secreting perforins and granzymes [4]. As a result, continuous proliferation and metastasis occur in the nearby organs.

An estimated 9.7 million people died from cancer in 2022, and there were 20 million new cases. 53.5 million people were expected to have survived a cancer diagnosis within five years [5]. In their lifetime, 1 in 5 people would have cancer, and 1 in 9 men and 1 in 12 women would die from the disease. Lung carcinoma was the common cancer occurring worldwide with 2.5 million new cases in 2022. The second most common is breast cancer with 2.3 million cases followed by colorectal cancer having 1.9 million cases [5]. The international research facilities have been trying to figure out and understand cancers with multiple clinical trials of treatment for over a decade [6].

In the Philippines, cancers have been the third leading cause of death among the Filipinos. A ratio of 184 Filipinos is diagnosed with cancer in every 100 000 individuals and 96 death-related cases were reported daily that was noted by the president of Philippine Society of Medical Oncology [7]. This data strengthens the idea of how cancers were dispersed internationally and locally, serving as a rationale for continued discovery and development against cancer cells.

Resveratrol is a naturally occurring polyphenol phytoalexin compound that is present in many plants such as grapes, berries, nuts, and pines [8]. A lot of studies have been associating resveratrol to possess anti-diabetic, cardioprotective, and anti-cancer properties against neuroblastoma, prostate cancer, breast cancer, and colon cancer [8]. Moreover, this compound also affects the molecular gene expression of miRNAs thereby regulating the proliferation of cancer through generating tumor suppressing agent — miRNAs (miR-424, miR-34a, and miR-503) by means of p53 pathway [9].

Study purpose

This research provides updated coverage of resveratrol's cytotoxic and cytostatic effects on cancer cells, offering valuable insights into its potential as a therapeutic agent. Through intensive research, the findings could possibly contribute to the development of more effective cancer treatments.

Moreover, this serves as a guide for researchers in designing future studies and in supporting clinicians in the exploration of novel treatment strategies.

Methodology for study determination

The researchers utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) flow diagram together with the established criteria of the following: studies should be exclusive to resveratrol only; published in Science Direct, PubMed, and MDPI and within the last 5 years; published articles written in English; primary research studies. Secondary research articles such as comparative analyses, editorials, duplicate studies and book reviews were excluded along with articles that focus on non-cytotoxic and non-cytostatic activity of resveratrol.

This process helps the researchers to identify the included studies presumptively at a surface level only. A second screening was done to the selected studies by reading the abstract, introduction, and methods of analysis using the Critical Appraisal Checklist (CASP). Since the study focused on research articles that explore mainly in vivo and in vitro studies, CASP's checklist for experimental studies was used as it is the most appropriate. The criterion given would be answered by yes, no, or unclear, and it would be recorded along with the rationale to evaluate the studies' validity for the review.

The following procedures were utilized to synthesize and integrate information: study categorization for coherent and clear synthesis, followed by graphs and tables to represent the data, and thematic analysis [10].

2. FINDINGS AND DISCUSSION

2.1 PRISMA-ScR

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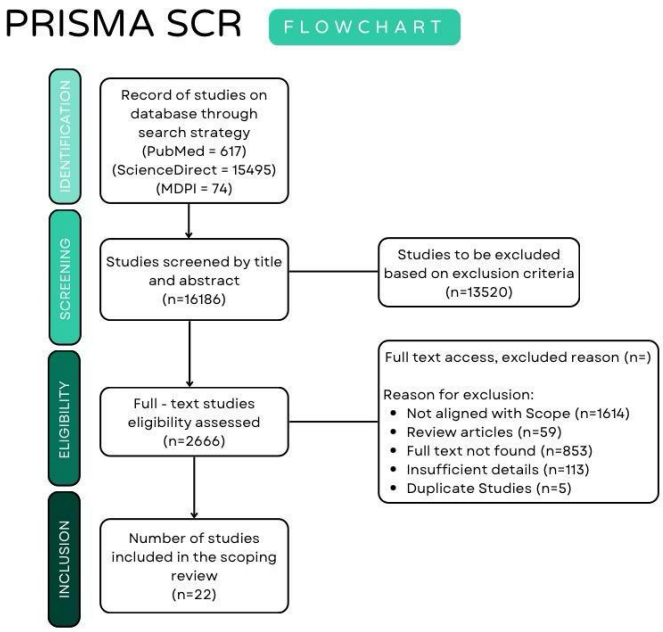

Figure 1: This figure shows the PRISMA-ScR, illustrating the process for the selection of appropriate studies.

The PRISMA-ScR flow diagram was followed as the basis for the selection process of the suitable research articles. The PRISMA flow diagram involves 4 phases: identification, screening, eligibility, and inclusion. Following the PRISMA-Scr, the total number of remaining studies aligned with the criteria and objectives would be recorded. Only 22 studies were deemed to be appropriate for the review. These studies underwent the Critical Appraisal Skills Programme (CASP) checklist, which led to a total of 13 final studies for the review.

2.2 Current Progress of Resveratrol

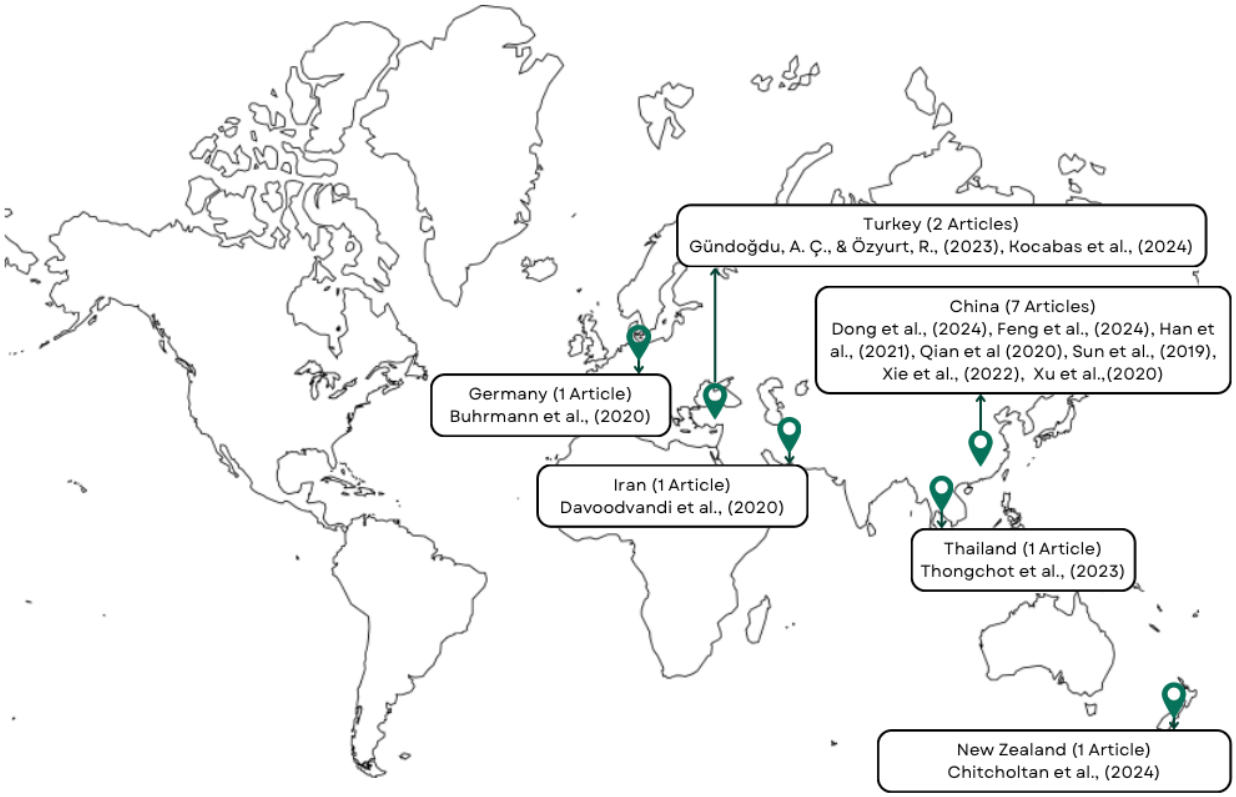

Figure 2: This figure shows the geography of the 13 chosen articles.

Figure 2 is a visual representation of the distribution of the 13 garnered final research articles across different countries. Markers were included for each country for the corresponding articles counted and cited. The distribution shows that China accumulated 7 studies, the highest number of articles, indicating the understanding and strong research presence on the topic. Turkey then followed with 2 research articles. Lastly, Germany, Iran, Thailand, and New Zealand each have 1 article. The variety of countries contributing suggests the interest in the topic, progression, advancement, and spread of resveratrol as a topic for research.

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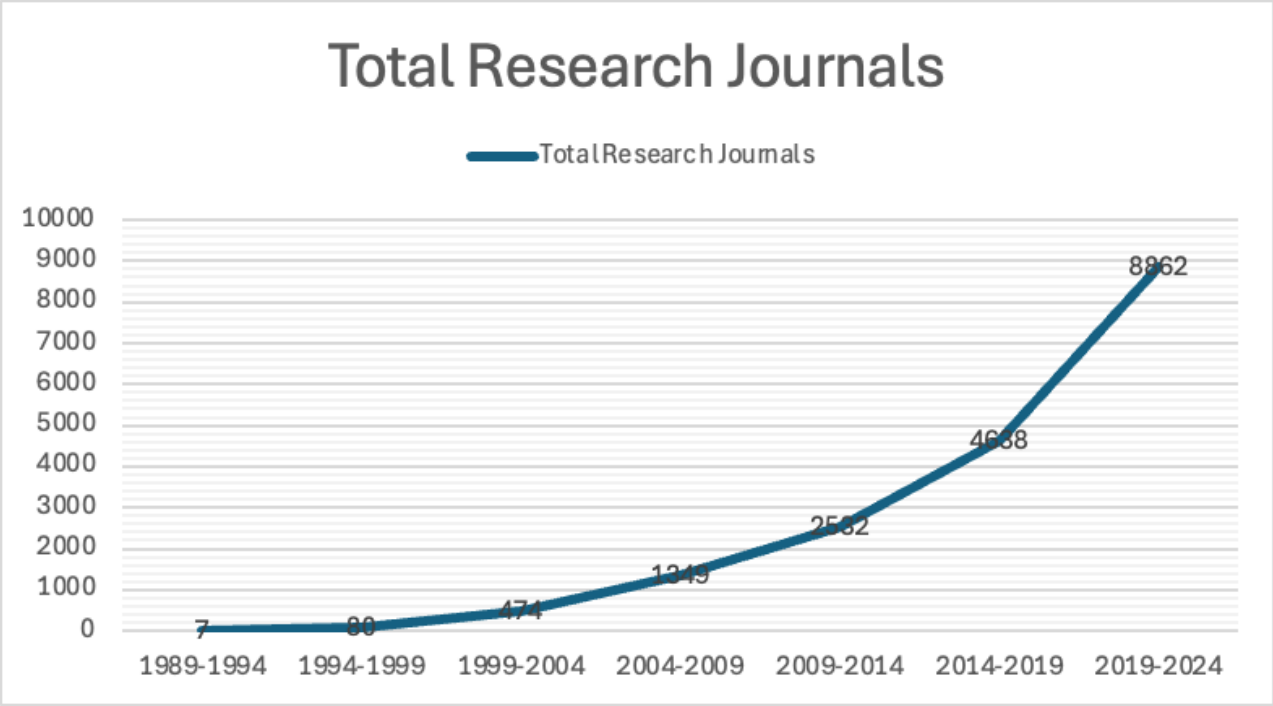

Figure 3: This figure shows the trend in research publications on Resveratrol's cytotoxic and cytostatic activity.

Resveratrol (3,4',5-trihydroxy-*trans*-stilbene) is a polyphenol that was first isolated in 1939 by Michio Takaoka from *Veratrum grandiflorum* and was first discovered to have cancer chemopreventive properties in 1997 by Jung and colleagues [11]. Figure 3 shows the consistent increase in the research journals published that studied the cytotoxic and cytostatic activity of resveratrol from 1989 to 2024. The number of journals published was at its lowest from 1989 to 1994 while the publication rate significantly increased during the following years, reaching its peak from 2019 to 2024. As the trend steadily increased, it indicated heightened interest in the field and technological advancements, ultimately revealing its promising role in cancer treatment.

The increasing number of research journals published over time can be attributed to the growing interest in cancer research that led to the advancements in the technologies involved in diagnosing and treating cancer. The cancer death rate over the years has continued to decline due to the emerging technologies resulting from cancer research, such as the improvement of cancer treatment precision and further understanding of the different causes of cancer [12]. Furthermore, the ongoing search for a cure for cancer has led to the discovery of different compounds that can be used to treat the said disease with minimal side effects, such as resveratrol.

Although the rising significance and relevance of resveratrol in cancer research in terms of *in vitro* studies and animal experiments have been promising, the limited development and use of resveratrol in clinical settings have been attributed to the compound's limited bioavailability, as it is rapidly metabolically eliminated in the bloodstream [11]. Moreover, the understanding of the molecular mechanism of action of resveratrol is still evolving, requiring further study and evaluation [13].

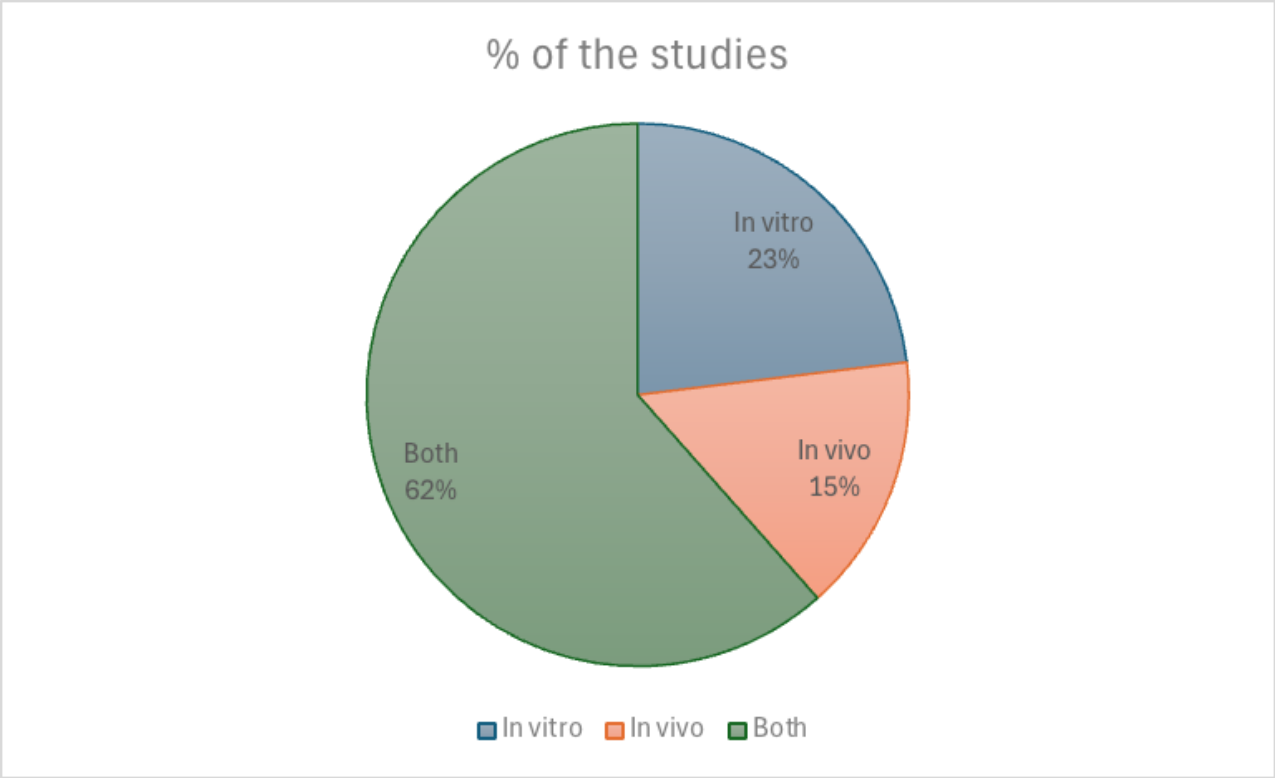

Figure 4: This figure shows the distribution of the compiled results of in vitro, in vivo, or both studies.

The in vitro and in vivo studies have been important in biochemical research for years in terms of examining drug interactions and disease processes and monitoring biological research in living organisms [14]. In vivo studies include the assessment of biological performance and the use of disease models in experimental animals [15]. Meanwhile, in vitro studies, a more cost-efficient substitute for in vivo experiments, studies were conducted in a controlled environment outside organisms, such as petri dishes [16]. However, the weakness lies in the uncertainty that can occur in a complex living organism [16].

Based on Figure 4, 8 out of 13 studies involved both in vitro and in vivo experiments, while 3 studies utilized in vitro methods, and the remaining 2 only conducted in vivo experiments. The study showed that resveratrol has both cytotoxic and cytostatic mechanisms that leads to apoptosis and inhibition of cell growth [17], [18].

The results suggest that resveratrol shows promising progress, as both in vivo and in vitro experiments have provided positive findings and validation for its therapeutic potential. Since in vivo studies were conducted on mouse models, there is an urge for human clinical trials to confirm the efficacy and therapeutic potential of resveratrol [19].

2.3 Cytotoxic Activity of Resveratrol

2.3.1 Dosage and Concentration

Table 1: Cytotoxic Activity of Resveratrol and Its Doses/Concentrations

Study	Dose/Concentration
[17]	100 µM

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Han et al., (2021)	12.5 mg/kg
Feng et al., (2024)	15.62 µM
Dong et al., (2024)	Dose: 5 mg/kg Concentration: 40 µM (AGS); 80 µM (HGC-27)
Kocabas et al., (2024)	46.8 µM (48h) and 18.7 µM (72h)
Thongchot et al., (2024)	Concentration: Group A: untreated. Group B: 50 mg/kg, (2 weeks before tumor inoculation.) Group C: 50 mg/kg after 1 week of tumor injection.

A study by Thongchot et al. administered 50 mg/kg of resveratrol in cholangiocarcinoma, which resulted in apoptosis [20]. Similarly, Han et al. administered 12.5 mg/kg of body weight for in vivo studies resulting in apoptosis of colon cancer cell lines [21]. A collection of in vitro studies utilized a range of concentrations between 15.62 µM to 100 µM. All in vitro studies with those ranging concentrations successfully induced apoptosis in cancer cell lines. For both in vivo and in vitro studies, as per Dong et al. utilized 40 µM and 80 µM for in vitro studies while 5 mg/kg for in vivo studies also induced apoptosis in gastric cancer cell lines [22].

Although there were no standard concentrations and dosages to be administered, some studies suggest that the cytotoxic effect of resveratrol needs to be greater than 80 µM [23]. Overall, the range of dosage utilized is 5mg/kg-50mg/kg while for dosage is 15.62 µM-100 µM. Given the results of the study, it strongly suggests that resveratrol can exert cytotoxic effects within those ranges inducing apoptosis in a wide variety of cancer cells. This means that it possesses a potential therapeutic agent as it demonstrates a good outcome based on table 1.

2.3.2 Target

Table 2. Cytotoxic Activity of Resveratrol and Its Targets

Study	Target
[17]	Colon cancer cell lines (HCT116 and HT29)
Han et al., (2021)	Triple negative breast cancer cell
Feng et al., (2024)	Hepatocellular carcinoma cell line (HepG2)
Dong et al., (2024)	Gastric cancer cell line (AGS and HGC-27)
Kocabas et al., (2024)	Human thyroid papillary carcinoma cell line (B-CPAP)
Thongchot et al., (2024)	Cholangiocarcinoma (CCA)

The in vitro studies reviewed have focused on various cancer cell lines to assess the cytotoxic effects of resveratrol and its potential therapeutic applications. [17] conducted research on colon cancer cell lines (HCT116 and HT29) to determine how resveratrol induces apoptosis. Similarly, Han et al. examined triple-negative breast cancer cells, evaluating how immune modulation enhances cytotoxicity [21]. Whereas, Feng et al. investigated hepatocellular carcinoma (HepG2), exploring how resveratrol affects cell cycle

progression [19]. Dong et al. studied gastric cancer (AGS & HGC-27) to determine whether apoptotic pathways were activated [22]. Kocabas et al. focused on thyroid papillary carcinoma (B-CPAP), assessing the effects of resveratrol on key signaling molecules [24]. Lastly, Thongchot et al. conducted an in vitro study on cholangiocarcinoma (CCA) to evaluate the involvement of autophagy in cancer suppression [20]. On the other hand, the in vivo studies of Han et al., Dong et al., and Thongchot et al., used xenograft tumor models of mice to conduct their experiments [20- 22]. Overall, this highlights the widened capacity of resveratrol to target different cancer cell lines possessing a great scope for therapeutics.

Among the 6 studies reviewed, 4 of them relate to gastrointestinal malignancies, mainly colon cancer, hepatocellular carcinoma, gastric cancer, and cholangiocarcinoma. This implies that resveratrol's cytotoxic activity may hold significant findings in this type of cancer. Although its specificity on cancer cell types remains unclear and under investigation, a study by Ren et al., which focuses on challenges and future recommendations on resveratrol, found that most studies give promising results for treatment in colorectal and obesity-related cancers [25]. These similar findings can further support the hypothesis that resveratrol's potential cytotoxic effects may offer significant therapeutic potential, especially for gastrointestinal-related cancers.

2.3.3 Pathways Involved

Table 3. Cytotoxic Activity of Resveratrol and Its Pathways

Study	Pathways Involved
[17]	Intrinsic (mitochondrial) apoptotic pathway, as evidenced by increased expression of Caspase-3 and Caspase-9. Activation of AMPK signaling pathway
Han et al., (2021)	Increased cytotoxic activity of CD8 T cells and Th1 immune response by downregulating PD-1 expression
Feng et al., (2024)	Modulation of the MALAT1/miR-143-3p/RRM2 axis, reduction of CDK2 and CCNB1 expression
Dong et al., (2024)	Downregulation of p-Akt expression, inhibition of PI3K-Akt signaling pathway by upregulation of P53 expression
Kocabas et al., (2024)	Inhibition of MAPK pathway via reduction of BRAF and ERK expression, increased NIS mRNA expression
Thongchot et al., (2024)	Downregulation of IL-6R/STAT3 pathway along with high BECLIN-1-dependent autophagy display a longer overall survival.

The reviewed studies identified multiple molecular pathways implicated in the cytotoxic effects of resveratrol across different cancer types. [17] demonstrated that in colon cancer, resveratrol activates the intrinsic (mitochondrial) apoptotic pathway, upregulating Caspase-3 and Caspase-9, which were key mediators of apoptosis. In the same study, the AMPK signaling pathway was activated, regulating cellular energy and promoting apoptosis. Activation of the AMPK pathway also inhibits the mTORC1 pathway which is primarily involved in cell growth and survival. This aligns with the study by Konieczny et al., stating that the AMPK pathway is dysregulated and reduced when cancer cells progress having the ability to metastasize in other areas of the body [26].

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Feng et al. found that in hepatocellular carcinoma, resveratrol modulated the MALAT1/miR-143-3p/RRM2 axis, leading to CDK2 and CCNB1 downregulation and subsequent cell cycle arrest in the S and G2 phases [19]. CDK2 is primarily involved in the transition of the G1 phase to the S phase where it facilitates the phosphorylation of key proteins for DNA synthesis through complex formation with cyclin E. Whereas, CCNB1 facilitates the G2 to M phase via the formation of complex with CDK1 which triggers mitosis. When MALAT1 is activated, it suppresses these genes from expressing products thereby, halting the process of synthesis and mitosis. However, a study by Arun et al. contradicts this as MALAT1 does the reverse process by increasing the migration and proliferation of breast cancer cells by binding the promoter called *EEF1A1* [27]. These contrasting findings suggest that this type of pathway is diverse and dependent on a type of cancer cell. The pathway should be taken into consideration as it appears to suppress hepatocellular carcinoma while upregulated in breast cancer.

Han et al. investigated triple-negative breast cancer, where resveratrol enhanced the Th1 immune response by downregulating PD-1 expression, thereby increasing CD8+ T cell cytotoxicity [21]. CD8+ T cells are known to have anti-tumor properties as they are involved mainly in killing malignant cells. These cells release certain cytokines, perforins, and granzymes in a denser amount to kill or lyse the tumor cells. Downregulation of PD-1 on the surface of CD8+ T cells avoids the interaction with PD-L1 thereby increasing the cytotoxicity.

In gastric cancer, Dong et al. reported that resveratrol suppressed the PI3K-Akt pathway through P53 upregulation, contributing to apoptosis [22]. PI3K-Akt pathway contributes to the metabolism, survival, and growth of cells. When resveratrol is administered p53 is upregulated suppressing the pathway leading to apoptosis of gastric cancer cells. Relation to this pathway has been targeted for therapeutical agents and as of now there are several drugs that target PI3K/ATK that is currently in the phase of clinical trials for hematologic malignancies and solid tumors making this pathway to be a door for treating cancer cells in the future [28].

Kocabas et al. found that in thyroid papillary carcinoma, resveratrol inhibited the MAPK pathway by downregulating BRAF and ERK expression, leading to reduced cancer cell survival [24]. Additionally, the study reported that NIS mRNA expression was upregulated, suggesting therapeutic potential for thyroid cancer. Lastly, Thongchot et al. explored cholangiocarcinoma, where resveratrol downregulated the IL-6R/STAT3 pathway and induced BECLIN-1-dependent autophagy, demonstrating both apoptosis and autophagy in cancer suppression [20]. The findings align with Esposito et al. showing that the IL-6R pathway has the potential to inhibit autophagy in ovarian cancer cell lines by decreasing the regulation of ARH-I [29]. The pathway possesses pro-growth effects, and it was found out in their study that resveratrol contrasts these effects keeping the cancer cells in an autophagy-mediated dormant-like state. Although different cancer cells were used in the study, the concept ties with each other that resveratrol can affect the IL-6R/STAT3 pathway making this organic compound an effective treatment for a wide variety of cancer cells.

2.3.4 Outcome

Table 4. Cytotoxic Activity of Resveratrol and Its Outcomes

Study	Outcome
[17]	Apoptosis
Han et al., (2021)	Apoptosis

Feng et al., (2024)	Promote cell cycle arrest in S and G2 phase, enhance apoptosis
Dong et al., (2024)	Apoptosis
Kocabas et al., (2024)	Apoptosis
Thongchot et al., (2024)	Apoptosis

Five studies exhibited apoptosis as the primary outcome to induce cytotoxicity in cancer cells mainly, colon cancer, triple-negative breast cancer, gastric cancer, thyroid papillary carcinoma, and cholangiocarcinoma. Meanwhile, one study about hepatocellular carcinoma utilized cell cycle arrest to inhibit cancer progression and also promote apoptosis. These findings suggest that resveratrol exerts its anticancer effects primarily through different apoptotic pathways, with additional evidence supporting its role in disrupting the cancer cell cycle. Moreover, the findings across all studies imply that resveratrol exhibits significant cytotoxic effects depending on the cancer type studied.

These findings align with the study of Jang et al. about the mechanisms of action of resveratrol [30]. According to this study, resveratrol promotes programmed cell death through various cytotoxic mechanisms which include apoptosis, autophagy, and necroptosis. Consistent with the findings of [17] in colon cancer and Dong et al. in gastric cancer, the review of Jang et al., also indicates that resveratrol effectively triggers apoptosis by activating intrinsic and extrinsic apoptotic pathways [22], [30]. Additionally, the findings of Feng et al. in hepatocellular carcinoma also support the review's results about cell cycle arrest as a mechanism of resveratrol's cytotoxic activity [19]. As observed in the work of Thongchot et al. on cholangiocarcinoma, the review also emphasizes the involvement of autophagy in cancer suppression [20]. By reviewing these mechanisms, the study of Jang et al. further supports the findings of this study [30].

2.4 Cytostatic Activity of Resveratrol

2.4.1 Dosage and Concentration

Table 5. Cytostatic Activity of Resveratrol and Its Dosages/Concentrations

Study	Dose/Concentration
Davoodvandi et al., (2020)	Dosage: 40 mg/kg
Xie et al., (2022)	Concentration: 12.5µM–50 µM Dosage: 120 mg/kg
Xu et al., (2020)	Concentration: 199.23 µM and 301.56 µM
Buhrmann et al., (2020)	Concentrations: 1, 2, 5, and 10 µM
Chitcholtan et al., (2024)	Dosage: 0.228 µg, 0.456 µg, 45.6 µg, 91.24 µg, and 182.4
Sun et al., (2019)	Concentrations: 12.5, 25, and 50 µM. Dosage: 40 mg/kg
Qian et al., (2020)	Concentration: 50 µM for acinar cells Dosage: 50 mg/kg/day for mice
Thongchot et al., (2023)	Dosage: 50 mg/kg

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In vivo research employed dosage to determine the total quantity of resveratrol provided in various animal models over a given period. Meanwhile, concentration was employed for in vitro research to determine the specific volume of resveratrol in a solution. Based on Figure 8, results have shown resveratrol dosage with a range of 0.228 mg/kg - 182.4 mg/kg with most of the studies having usually used 40 mg/kg and 50 mg/kg. As for concentration, the range is around 1 - 301.56 µM, with a frequently used 50 µM. In the study of Qian et al., resveratrol was proven to have an effect in vivo with a dosage of 50 mg/kg on pancreatic cancer by slowing tumorigenesis, as resveratrol may inhibit the activation of the NF-kB pathway [31]. In addition, the study of Xie et al. showed that 50 µM was the most effective for in vivo study against various cancer stem cells [32]. It is critical to understand the concentration and dosage utilized so that future researchers can use it as a reference to produce relevant results that were consistent with human patients in future clinical studies [33].

2.4.2 Target

Table 6. Cytostatic Activity of Resveratrol and Its Targets

Study	Target
Davoodvandi et al., (2020)	Lung cancer cells
Xie et al., (2022)	Human normal bronchial epithelial cells (HBE) and lung cancer cell lines (A549, NCI-H460, NCI-H226 and NCI-H1299)
Xu et al., (2020)	Follicular thyroid cancer cells
Buhrmann et al., (2020)	A human colorectal cancer cell line, HCT116, a normal human fibroblast cell line (MRC-5) and a human T-lymphocytes cell line (Jurkat Cells)
Chitcholtan et al., (2024)	Ovarian cancer cell lines: OVCAR-8 and SKOV-3
Sun et al., (2019)	MDA-MB-231 (MDA231) human breast cancer cells
Qian et al., (2020)	Pancreatic cancer cell
Thongchot et al., (2023)	Cholangiocarcinoma (CCA)

The 8 studies focusing on the cytostatic effect of resveratrol targeted various cancer cell lines, indicating that resveratrol can cover a wide range of malignancies. Two studies focused on lung cancer cells: Davoodvandi et al. used resveratrol on unspecified lung cancer cells, while Xie et al. examined its impact on multiple cancer cell lines (A549, NCl-H460, NCl-H226, and NCl-H1299) and normal bronchial epithelial cells (HBE) [18], [32]. Aside from these, the study by Hu et al. explored resveratrol's effects on follicular thyroid cancer cells, while Buhrmann et al. used resveratrol to target HCT116 cell line, normal human fibroblasts (MRC-5), and Jurkat T-lymphocytes to study its impact on colorectal cancer [34], [35]. Meanwhile, the study by Chitcholtan et al. investigated resveratrol's action in ovarian cancer using OVCAR-8 and SKOV-3 cell lines, whereas Sun et al. focused on breast cancer (MDA-MB-231) [36], [37]. The last two studies by Qian et al. and Thongchot et al. examined resveratrol's effects on pancreatic cancer cells in KC mice and cholangiocarcinoma, respectively [20], [31].

Based on Figure 6, lung cancer was the most frequently studied having two authors investigating the effects of resveratrol [18], [32]. Between the two studies, a unique feature of Xie et al.'s study is the inclusion of normal bronchial epithelial cells along with the pathologic cells [32]. Similarly, it also evaluated normal fibroblasts and Jurkat T-lymphocytes alongside colorectal cancer cells, making it one of the few studies to compare resveratrol's impact on cancerous and non-cancerous cell lines [35]. The results suggested that resveratrol exerts its cytostatic effects on colorectal cancer cells, with minimal impact on normal fibroblasts and immune cells. With aforementioned studies, their results helped explore the potential selective cytostatic activity of resveratrol, having the ability of targeting malignant cells while keeping the normal ones unaffected, which is an essential factor in determining clinical utility. However, this discovery is challenged by the results of Qian et al.'s study on pancreatic cancer using a KC mouse model [31]. The findings suggest that resveratrol may alter the tumor microenvironment, affecting both cancerous and surrounding non-cancerous cells.

The other four studies each focused on single cancer types, namely breast, ovarian, cholangiocarcinoma, and follicular thyroid cancer [20], [36- 38]. Sun et al. studied the MDA-MB-231 cell line, a model for highly aggressive triple-negative breast cancer (TNBC) [37]. It is particularly challenging to treat due to the lack of hormone receptor targets, but the study highlighted resveratrol's relevance as a potential adjunct therapy. Meanwhile, Chitcholtan et al. studied resveratrol's effects on ovarian cancer by utilizing two aggressive cancer cell lines: OVCAR-8 and SKOV-3 [36]. Considering that ovarian cancer remains one of the challenging malignancies, the study's results have shown that resveratrol has a potentially great activity against a cancer type that often exhibits therapeutic resistance.

Another study led by Thongchot et al. investigated resveratrol's effects on cholangiocarcinoma, a rare and highly aggressive bile duct cancer [20]. With the limited treatment options, the study provided new insight into resveratrol's broader applications and its role in this cancer type. Finally, only Xu et al. studied resveratrol's effects on follicular thyroid cancer, which has a distinct tumorigenic mechanism among other cancers requiring different therapeutic approaches [38]. This highlights the potential broad application of resveratrol in modulating thyroid cancer-specific pathways.

Among all of the eight studies included, resveratrol demonstrated significant cytostatic effects across multiple cancer types discussed above. The inclusion of normal cells in some studies also helped strengthen the argument for its selective anticancer properties, while the diversity of targeted malignancies highlights its broad therapeutic potential.

2.4.3 Pathways Involved

Table 7. Cytostatic Activity of Resveratrol and Its Pathways

Study	Pathways
Davoodvandi et al., (2020)	Upregulation of CXCL10 and IFN-y as immunomodulation, angiogenesis inhibition through dysregulation of (VASP, VEGF, COX2, VASSP)
Xie et al., (2022)	Downregulation of the Wnt/β-catenin signaling pathway. Inhibition of the pro-inflammatory cytokine IL-6 in the tumor microenvironment.

	IL-6 and Wnt/β-catenin pathway interaction.
Xu et al., (2020)	Inhibition of ST6GAL2 expression thereby activating Hippo signaling pathway (prevents tumorigenesis of follicular thyroid carcinoma)
Buhrmann et al., (2020)	Suppression of NF-κB signaling Downregulation of biomarkers such as CD133, CD44, and ALDH1 in cancer stem cell pathways.
Chitcholtan et al., (2024)	Reduction of phosphorylation of NF-κB (pNF-κB) signaling molecule Reduction of expression of SLUG protein
Sun et al., (2019)	Reversed TGF-β1-induced Epithelial-to-mesenchymal transition (EMT) through inhibition of PI3K/AKT and Smad signaling pathways. Downregulation of EMT Markers and decreased expression and secretion of MMP-2 and MMP-9
Qian et al., (2020)	Decreased the NFκB-targeting genes such as Cox2 (a pro-inflammatory marker), CyclinD1 (a proliferation marker), Bcl2 (an anti-apoptosis marker) and MMP9 (a metastasis marker) levels in KC mouse pancreatic precancerous lesion that indicates inhibition of NFκB activation Reduced levels of p-ERK and p-STAT3 in KC mouse pancreatic precancerous lesions (inhibition of STAT3 & ERK signaling pathway activation)
Thongchot et al., (2023)	Downregulation of IL-6R/STAT3 pathway along with high BECLIN-1-dependent autophagy display a longer overall survival.

The studies reviewed demonstrated that resveratrol exerts its cytostatic effects through multiple molecular pathways, which target key mechanisms involved in cancer cell proliferation, inflammation, angiogenesis, and metastasis. Three among eight studies highlighted resveratrol's inflammatory signaling inhibition through the NF-κB suppression. The nuclear factor kappa B (NF-κB) signaling pathway is linked to pathological and physiological processes, including inflammation, immune response, and tumorigenesis [39]. Through this pathway, Buhrmann et al. not only revealed the inflammatory reduction activity of resveratrol but also noted a downregulation of cancer stem cell markers (CD133, CD44, ALDH1) which help suppress cancer stemness—a key factor in tumor recurrence [35]. In contrast, Chitcholtan et al. revealed resveratrol's ability to downregulate SLUG, which is a transcription factor involved in epithelial-to-mesenchymal transition (EMT), suggesting its metastasis-inhibiting function [36]. Finally, it was observed that NF-κB suppression led to decreased expression of pro-inflammatory and pro-survival genes (Cox-2, Cyclin D1, Bcl-2, MMP-9) that aid in reducing tumor cell proliferation and survival [31]. Despite the differences in the results, all three studies still demonstrated resveratrol's cytostatic activity via the NF-κB inhibition pathway.

Another pathway is the STAT3 signaling pathway, which was inhibited in both Qian et al.'s study on pancreatic cancer and Thongchot et al.'s study on cholangiocarcinoma [20], [31]. STAT3 is a well-known promoter of tumor growth by inhibiting cell apoptosis and immune evasion by promoting the immunosuppression of tumor-associated macrophages and myeloid-derived suppressor cells [34]. Both studies by the aforementioned authors demonstrated the inhibition of the STAT3 signaling pathway, suggesting resveratrol's role as an anti-inflammatory and anti-proliferative agent. Specifically, Thongchot et al. linked the inhibition of STAT3 to increased BECLIN-1-mediated autophagy [20].

According to Zhang et al., the EMT is a physiological process whereby epithelial-like features of epithelial cells are reduced, such as their plasticity and intercellular adhesion, and migrate to invasive mesenchymal cells [40]. Additionally, several studies stated that EMT is related to drug resistance in cancer cells. Sun et al. demonstrated that resveratrol reversed TGF-β1-induced epithelial-to-mesenchymal transition (EMT) via inhibition of PI3K/AKT and Smad pathways reduced EMT markers and MMP-2/MMP-9 expression [37]. Similarly, as discussed in the preceding paragraphs, Chitcholtan et al. found that resveratrol reduced phosphorylation of NF-κB which downregulated the SLUG expression—a transcription factor involved in epithelial-to-mesenchymal transition (EMT) [36].

In contrast to these EMT-focused studies, Xu et al. (thyroid cancer) identified a completely different tumor-suppressive mechanism involving Hippo pathway activation [38]. This study found that resveratrol inhibited ST6GAL2 expression, leading to the activation of the Hippo pathway, which plays a role in organ size regulation and tumor suppression. Meanwhile, two studies specifically investigated Wnt/β-catenin signaling and cancer stem cell inhibition: Xie et al. (lung cancer) and Buhrmann et al. (colorectal cancer) [32], [35]. Xie et al. demonstrated that resveratrol downregulated Wnt/β-catenin signaling in lung cancer cells, leading to reduced tumor growth and inflammation [32]. The study also highlighted the interaction between Wnt/β-catenin and IL-6, suggesting a link between inflammation and cancer progression. Buhrmann et al. focused on the suppression of cancer stem cell markers (CD133, CD44, ALDH1) in colorectal cancer, a finding that aligns with Wnt/β-catenin inhibition [35]. Although the two studies do not completely overlap in their findings, they both suggest that resveratrol may impair cancer progression by targeting pathways essential for stemness and tumor initiation.

2.4.4 Outcome

Table 8. Cytostatic Activity of Resveratrol and Its Outcomes

Study	Outcome
Davoodvandi et al., (2020)	Immune modulation Anti-angiogenesis
Xie et al., (2022)	Inhibition of proliferative signaling Immune modulation
Xu et al., (2020)	Slows tumorigenesis
Buhrmann et al., (2020)	Inhibition of proliferative signaling Epigenetic modulation Slows tumorigenesis
Chitcholtan et al., (2024)	Anti-angiogenesis
Sun et al., (2019)	Slows tumorigenesis

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Qian et al., (2020)	Slows tumorigenesis Inhibition of proliferative signaling
Thongchot et al., (2023)	Inhibition of proliferative signaling Autophagy

As shown in Table 8, the outcomes of resveratrol against cancer cells were inhibition of proliferative signaling, slowing tumorigenesis, anti-angiogenesis, immune modulation, autophagy, and epigenetic regulation. In 4 out of 8 studies, inhibiting proliferative signals has been shown to have the most outcome. Resveratrol induces inhibition of proliferative signaling, including the NFxB signaling, MAPK, Wnt/β-catenin signaling, and STAT3 signaling [31]. This finding is significant as it is crucial not to activate or alter these signaling pathways since they oversee the vital processes in cancer cells, including tumor growth progression, which favors cancer cell survival and leads to uncontrollable metastasis [41].

Meanwhile, 4 studies showed that resveratrol slows tumorigenesis. Resveratrol slows the progression of the transformation of cancer cells through inhibiting the signaling pathway [31]. This demonstrates that resveratrol's activity has a domino effect, leading to the occurrence of other mechanisms, which can be inferred that all actions are interconnected. Moreover, in a study by Liu et al. resveratrol was proven to inhibit spontaneous tumorigenesis in liver neoplasm by activating the SIRT 1 pathway leading to decrease in proliferation of cancer cells by inactivating K-Ras/PI3K/AKT pathway and deacetylation of K-Ras [39]. This shows the mechanism of action of resveratrol can slow tumorigenesis by inhibition or activation of various pathways to target cancer cells.

Next, 2 out of 8 studies exhibit anti-angiogenesis. Anti-angiogenesis deprives the tumor environment of further growth as it stops the blood supply that supports the growth of the cancer cells that results in pan-necrosis and pan-hypoxia in solid tumors [42]. This can be supported by the study of Sintuyanon et al. in head and neck cancer squamous cell carcinoma (HNSCC); resveratrol possesses an antiangiogenic property through the downregulation of vascular endothelial growth factor (VEGF) expression under a hypoxic environment, thereby reducing the migration of cancer cells [43].

Two studies showed that resveratrol can result in immune modulation. Immune modulation in which they modulate the secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) that stimulate the tumor to progress, metastasize, and grow [44]. In accordance with Lee et al., these cytokines are known to be associated with advanced stages of cancer, immunotherapy resistance, and having a poor prognosis as they contribute to the inflammatory tumor microenvironment along with chemokines, inflammatory cells, and signaling pathways [45].

Furthermore, only the study of Thongchot et al. proved that resveratrol is involved in autophagy [20]. Autophagy supports the body to maintain homeostasis during cancer as it removes damaged, toxic misfolded proteins and damaged organelles [46]. This slows tumorigenesis in the early stage of cancer as it limits the ROS production and DNA damage, but in the advanced stage, autophagy promotes the survival of these cancer cells and accelerates tumorigenesis [47].

Only 1 study has yielded epigenetic regulation. Resveratrol restricts the oncogenic function of the SIRT1 signaling axis, leading to epigenetic regulation in cancer cells [35]. Epigenetic regulation is crucial as it can be a double-edged sword in cancer progression and initiation, as it can alter the genes, such as histone modifications, DNA methylation, and non-coding RNAs, is reversible [48].

Overall, resveratrol's cytostatic mechanism focuses on inhibition of cell growth and suppressing cancer stem cells. The multiple cytostatic mechanisms of action of resveratrol demonstrated how promising it is as a possible therapeutic agent, as it can result in many outcomes targeting various cancer cells.

3. Conclusion

The results encompassing the cytotoxic and cytostatic activity of resveratrol in terms of dosage or concentration, target, pathways, and outcomes revealed its wide scope of therapeutics in oncology. In vivo and in vitro studies identified the underlying mechanisms of resveratrol against various cancer lines with the use of multiple assays showcasing its effectiveness in inhibiting the proliferation, growth, and metastasis of cancer cells in nearby tissues. Additionally, the current progress of Resveratrol highlights the increasing trend indicating heightened interest and technological advancements in the medical and research field.

In cytotoxic division, Resveratrol reinforced a promising result across various cancer cell lines, and these include colon, triple-negative breast, gastric, thyroid papillary, and cholangiocarcinoma. Strong and profound evidence is traced among its outcomes in inducing apoptosis through molecular pathways such as caspase activation, immunomodulation, mitochondrial dysfunction, and inhibiting signaling pathways like PI3K-Akt and MAPK.

In cytostatic division, it demonstrated slowed tumorigenesis and inhibited proliferation by targeting NF-κB, STAT3, Wnt/β-catenin, and PI3K/AKT pathways. While Resveratrol exhibits multiple effects against cancer cells, it is crucial to determine the standard concentration and dosage for clinical application. Further research is needed to determine its efficacy in humans being meticulous in administering this drug aiming at a preferred dosage for cancer therapies and worsened malignancies. Overall, Resveratrol as a polyphenol compound found in natural sources, such as grapes and berries, exhibited a good cytotoxic and cytostatic effects against various cancer cell lines advocating for extensive research in dosage and concentration for therapeutic applications in humans.

Conclusively, the researchers highlighted the following key points: First, sets of studies on Resveratrol indicated their dosage and concentration with a good outcome using various cancer cell lines compiling a non-standardized range of concentration. However, factors such as administration, cell size, and incubation may affect the results of the studies paving the way for intensive work in determining the standardized concentration should be considered. Lastly, some molecular mechanisms may have a contradicting action depending on the cancer cell lines used. Resveratrol may upregulate a certain pathway in a specific cancer cell line inhibiting proliferation while exhibiting the opposite effect on another cell line. This suggests a mechanistic exploration of signaling pathways among a diverse tumor microenvironment.

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