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Review Article

The small phytomolecule resveratrol: A promising role in boosting tumor cell chemosensitivity

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Abstract

Resveratrol (RES), chemically known as trans-3,5,4′-trihydroxystilbene, is a polyphenolic molecule that occurs naturally and is produced by a variety of plants in response to being stimulated by diverse stimuli. It possesses a wide range of biological activities and provides a multitude of health benefits, including anti-tumor, cardioprotective, anti-inflammatory, and antioxidant characteristics. According to the findings of research on the bioavailability of RES, oral administration results in a high level of absorption. However, research has demonstrated that the administration of RES through gavage or intravenous administration produces more favorable results than the administration of RES through oral administration. As a result, more research has been carried out to address the rapid metabolism of RES. This has been accomplished through the utilization of novel formulation methodologies, metabolic regulation, and the analysis of potential interactions with other dietary variables. Through the process of triggering apoptosis, RES has been proposed as a possible agent for reversing drug resistance and improving the therapeutic potential of chemotherapy. Additionally, RES exhibits promising antiproliferative properties when paired with chemotherapeutic medicines, which enhances the overall function of these treatments. It is vital to do additional research to shed light on the beneficial role that RES plays in the context of cancer therapy, even though there have been few clinical trials that combine RES with anticancer medications.

Keywords

resveratrol, bioavailability, multidrug resistance, anti-apoptotic activity, anti-proliferative activity

Introduction

Resveratrol's capacity to suppress cancer-promoting signaling pathways adds to its anticancer properties (Gupta et al. 2021). It is particularly prevalent in the skin of red grapes, red wine, peanuts, and berries. The potential health benefits that it possesses, such as its anti-inflammatory and antioxidant characteristics, have brought it to the forefront of public attention (Meng et al. 2020). Further investigation has been conducted to investigate its possible function in the prevention and treatment of cancer, including its influence on the chemosensitivity of

tumor cells. Previous research has indicated that resveratrol may possess anticancer effects through a variety of pathways (Rahman et al. 2012; Amini et al. 2023). Resveratrol possesses antioxidant characteristics, which refer to the fact that it could assist in the neutralization of potentially damaging free radicals within the body. It is possible that resveratrol can help prevent cancer by lowering the levels of oxidative stress in the body (Ding et al. 2023). The genesis and progression of cancer are both linked to chronic inflammation, which has been shown to induce anti-inflammatory effects (Santos et al. 2023). It has been demonstrated that resveratrol possesses anti-inflammatory properties, which may be a factor in its potential anticancer efficacy (Shahcheraghi et al. 2023). Resveratrol has been shown to promote apoptosis, which is a form of programmed cell death, in a few different cancer cell lines (Chimento et al. 2023). The process of limiting the uncontrolled proliferation of cancer cells is an essential step in the prevention of cancer (Wu et al. 2023). It has been proposed by several studies that resveratrol may be able to limit the proliferation of tumor cells, which would result in a reduction in the rate at which cancer is growing and spreading. Resveratrol has the potential to affect the degree to which tumor cells can respond to chemotherapy (Mirzaei et al. 2023). According to the findings of some studies, it has the potential to improve the efficacy of chemotherapeutic drugs, hence rendering cancer cells more amenable to therapy. There is data that supports the possible anticancer characteristics of resveratrol in laboratory research and animal models (Angellotti et al. 2023); however, the outcomes in human clinical trials have been mixed. There is still a lot of research and discussion going on over whether resveratrol is beneficial as a treatment for cancer on its own or as a supplement to more conventional treatments.

It is also possible that different people will react differently to resveratrol, and additional research is required to properly comprehend the role that it plays in the treatment of cancer. Beyond its direct effects on tumor cells, resveratrol modulates the tumor microenvironment (TME) (Li et al. 2023). The TME's complex interaction of stromal, immunological, and extracellular matrix cells affects cancer growth. Resveratrol's anti-inflammatory and immune-boosting effects reshape the TME to reduce cancer growth (Dariya et al. 2023). Resveratrol's dynamic interaction with the TME shows its potential to boost chemotherapy efficacy by generating a hostile environment for cancer cells (Xie et al. 2023). This review summarizes the present research in this sector, providing insights that may lead to future research and more effective and customized anticancer treatments. By understanding the molecular mechanisms behind resveratrol's chemosensitizing effects, we can maximize its cancer-fighting potential. In this review, the anti-apoptotic and antiproliferative effects of combining RES with chemotherapeutics and targeted therapies are highlighted, underscoring the significance of RES as an adjuvant in the treatment of cancer.

Resveratrol's chemical structure and properties

Resveratrol (RES), chemically known as 3,5,4'-trihydroxystilbene, is a natural polyphenolic compound produced by different plants (Gambini et al. 2015). It has been classified as a natural phytoalexin synthesized by plants in response to different injuries, including fungal attacks, UV irradiation, or ozone exposure (Hasan and Bae 2017). RES is biologically active and has beneficial pleiotropic health effects, including antioxidant, anti-inflammatory, cardioprotective, and anti-tumor properties (Kursvietiene et al. 2016). RES could be present as a cis- or trans-isomer, the latter being the most frequent and biologically active form (Fig. 1). However, RES is a highly photosensitive compound susceptible to UV-induced isomerization, since more than 80% of trans-RES in solution are converted into cis-RES upon exposure to light for one hour (Neves et al. 2012).

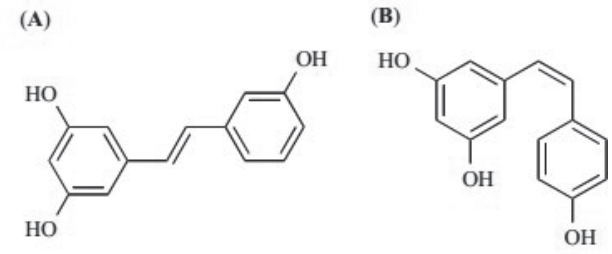

Figure 1. Chemical structures of resveratrol isomers. **A**. trans-3,5,4'-trihydroxystilbene, and **B**. cis-3,5,4'-trihydroxystilbene (Neves *et al.* 2012).

Resveratrol sources

RES sources include dried roots and the tea of Japanese knotweed (*Polygonum cuspidatum*), also called Ko-jokon in Japan, with numerous effects in traditional Chinese and Japanese medicine (inflammation, suppurative dermatitis, gonorrhea, favus, athlete's foot, allergy, heart diseases, and hyperlipidemia). RES has been identified in a variety of 70 plant species and fruits, including purple grapes, blueberries, mulberries, cranberries, rhubarb, peanuts, groundnuts, and pines, as well as coconut and cocoa (Neves et al. 2012).

Resveratrol's pharmacokinetics and pharmacodynamics

As RES pharmacology has been subjected to extensive studies during the past decade, its pharmacokinetics have also been investigated in preclinical models as well as in humans. Studies on RES bioavailability suggest its high-level absorption following oral administration. It is also rapidly metabolized at short-term doses without adverse effects, depending on the hepatic function and the

metabolic activity of the local intestinal microflora (Neves et al. 2012; Salehi et al. 2018). Oral RES administration results in a high-level metabolism, leading to low levels of circulating RES. RES administration by gavage yielded better results than oral consumption (Crowell et al. 2004). RES entry into the hepatic portal system leads to its metabolism, and while escaping, it might increase free plasmatic RES levels. Therefore, several studies have demonstrated that intravenous RES administration generates an increase in free RES levels in the plasma and helps maintain high RES levels. Moreover, to address rapid RES metabolism, nanoformulations could increase RES solubility and tissue absorption (Table 1).

RES is absorbed by the intestine with 77%–80% efficacy. Its metabolism occurs in the liver, generating glucoronide and sulfate derivates. In addition, RES is mainly (75%) excreted (Pannu and Bhatnagar 2019). It displays poor water solubility; it thus binds to plasma proteins, ensuring its body distribution and bioavailability. Several plasma proteins, such as lipoproteins, hemoglobin, and albumin, contribute to the cellular uptake and diffusion of RES through the plasma membrane. Interestingly, neither cytotoxicity nor cytolysis could be observed in hepatocytes after high-dose RES treatments (Neves et al. 2012). Interesting anticancer properties have been attributed to RES, mainly against various solid tumor types (Espinoza et al. 2012; Lucas et al. 2018; Mukherjee et al. 2018; Kim et al. 2019). The underlying molecular mechanisms of RES anticancer potential include cell viability reduction, cell cycle arrest, and apoptosis (Heo et al. 2018; Kim et al. 2019). Moreover, RES has shown promising results in immune cell stimulation (Mukherjee et al. 2018).

Despite these interesting properties, the clinical applications of RES remain limited due to its poor bioavailability. New strategies for formulations and metabolic regulation, as well as identifying its possible interactions with other dietary factors, would still be required to improve RES properties. Howels and collaborators evaluated the potential pharmacodynamic effects of micronized RES (SRT501) by comparing the expression and activation of candidate protein biomarkers intrinsically associated with cell survival and apoptosis in the circulation and tissue of patients receiving the agent versus placebo (Howells et al. 2011). The authors observed high-level (39%) apoptosis in patients taking SRT501 compared to the participants taking placebo.

However, RES exhibits several disadvantageous properties, such as poor water solubility, a short biological half-life, chemical instability (the tendency to suffer oxidation and extreme photosensitivity), and its extensive and rapid metabolism and elimination, justifying its encapsulation in carriers (Neves et al. 2012). Therefore, several carriers were used for RES encapsulation and delivery alone or with other drugs (Table 2). Lipid core nanocapsules provide better stability and increased concentration for RES. Another solution is preventing RES from metabolism by inhibiting glucoronidation and sulfation. Therefore, RES was supplemented with phenolic compounds that inhibit sulfotransferase 1A1 (SULT1A1) activity. Other synthetic polymers were used to improve RES solubility by increasing its absorption.

Resveratrol in combination with chemical drugs

Cancer therapeutic procedures generally include surgery, radiation therapy, chemotherapy, immunotherapy, and combined therapy. In most cancers, chemotherapy remains a promising treatment strategy because chemotherapeutic

Table 1. Bioavailability of resveratrol in different studied in vivo models.

	Resveratrol derivate	Administration route	Resveratrol concentration	Plasma concentration	References
Rats	Trans-resveratrol	oral	20mg/kg	1,2μM	(Asensi et al. 2002)
Male rats	Trans-resveratrol	by gavage	300-1000-3000mg/kg	576-991-2728 ng/ml	(Crowell et al. 2004)
Female rats	Trans-resveratrol	by gavage	300-1000-3000	333-704-1137 ng/ml	(Crowell et al. 2004)
Rats	resveratrol	oral	2 mg/kg	1,2 μM	(Meng et al. 2004)
		intravenous oral	15 mg/kg	15,2 μg/ml	(Penalva et al. 2018)
		oral suspension	15 mg/kg	0,20 μg/ml	(Penalva et al. 2018)
		loaded in casein	15 mg/kg	–	(Penalva et al. 2018)
		nanoparticles	15 mg/kg	0,29 μg/ml	(Penalva et al. 2018)
Human	Trans-resveratrol	oral	25, 50, 100 and 150 mg,	3.89, 7.39, 23.1 and 63.8 ng/mL	(Almeida et al. 2009)
		oral	25mg	2μM	(Neves et al. 2012)
		Oral (Powder (original)	40 mg	470 nM	(Amiot et al. 2013
		Oral (Soluble innovative form)	40 mg	5707 nM	(Amiot et al. 2013)
		Oral	500 mg	71,181 ng/ml	(Sergides et al. 2016)
	resveratrol	Oral	180 mg	2 μM	(Iannitti et al. 2020)
	Resv@MDH (Solid Dispersion of Resveratrol Supported by Magnesium Di Hydroxide formulation)	Oral	180 mg	6 μM	(Iannitti et al. 2020)

Table 2. Carriers used for the encapsulation and delivery of resveratrol and other drugs.

Carrier type	Drug	Targeted cancer	Major effects	References
pluronic® f127 micelles (mrq)	Doxoru bicin hydroc hloride (ADR)	human ovarian cancer cells (SKOV-3)	-maintaining or increasing the efficacy of ADR against cancer cell lines in vitro. -being cardioprotective in vitro and in vivo	(Cote et al. 2015)
combinations of micellar resveratrol (r) with quercetin (q) (mrq) or r: curcumin (c) (mrc)	Adriam ycin	Ovarian cancer cells (ES2-Luc, A2780ADR)	- reducing Adriamycin dosing through chemosensitization while being cardioprotective.	(Fatease et al. 2019)
holo-transferrin conjugated liposomes for sirna delivery, and electrospun polycaprolactone (pcl)- gelatin (gt) microfibers for resveratrol	Targete d siRNA	K562 cells	-Targeted siRNA release in combination with resveratrol release was more potent and has long-term effects compared to bolus doses. -increasing K562 cells non- viability level.	(Al-Attar and Madihally 2019)
silver nanoparticles (agnps) using resveratrol as a reducing and stabilizing agent	Gemcit abine (GEM)	human ovarian cancer cell line A2780	-exhibiting potent apoptotic activity in human ovarian cancer cells. -inhibiting viability and proliferation in A2780 cells.	(Yuan et al. 2017)
hot melt extruded solid dispersion of tamoxifen citrate and resveratrol	Tamoxi fen	MCF-7 breast cancer cells	-showing significantly lower IC50 compared to Tamoxifen with increasing ratio of RES which is a result of apoptosis.	(Chowdhury et al. 2018)
planetary ball milled (pbm) nanoparticles (nps) encapsulated with resveratrol (res)	docetax el (DTX)	Prostate cancer (PCa)	-increasing in the number of apoptotic cells. -exhibiting additional cytotoxic effects with the down-regulation of survivin and an increased expression of Cleaved Caspase-3 in PCa cells.	(Singh et al. 2018)
lyotropic liquid crystalline nanoparticles (lcnps) : carriers for co-delivery of pemetrexed and resveratrol (pmx-rsv-lcnps)	pemetr exed	A549 lung cancer cells	-inhibiting tumor growth, angiogenesis and induction of apoptosis.	(Abdelaziz et al. 2019)
temozolomide and resveratrol were loaded simultaneously into nanoparticles with methoxy poly(ethylene glycol)-poly epsilon caprolactone (mpeg-pcl)		U87 glioma cells	-inducing higher apoptosis in U87 glioma. inhibiting phosphor-Akt, leading to upregulation of the downstream apoptotic proteins. -superior tumor delaying effect that of free drug combination.	(Xu et al. 2017)
ursodeoxycholic acid (udca) as a hepatoprotective agent was grafted to maltodextrin (md) via carbodiimide coupling to develop amphiphilic maltodextrin- ursodeoxycholic acid (mdca)-based micelles. sulfasalazine (ssz), as a novel anticancer agent, was conjugated via a tumor-cleavable	Sulfasa lazine temozo lomide	Hepatocellular Carcinoma	-enhancing cytotoxicity and internalizating into HepG-2 liver cancer cells via binding to overexpressed folate and asialoglycoprotein receptors. - reducing the liver/body weight ratio, inhibiting the angiogenesis, and enhancing apoptosis.	(Anwar et al. 2018)
ester bond to md backbone to obtain tumor-specific release, whereas resveratrol (rsv) was physically entrapped within the hydrophobic micellar core. both folic acid (fa) and lactobionic acid (la) were coupled to the surface of micelles to obtain dual-targeted micelles.				

drugs can eradicate cancer by inducing tumor cell apoptosis (Luqmani 2005). Drug resistance is a common concern, deeply hampering the treatment of numerous tumors. Frequently, resistance to a single chemotherapeutic agent could induce cross-resistance to various structurally and functionally different drugs, representing multidrug resistance (MDR) (Young et al. 2001). RES has been proposed as an agent potentially reversing drug resistance and improving chemotherapeutic potential. Interestingly, combined with chemotherapeutic drugs, RES could provide a beneficial novel strategy. Here we describe studies with strong circumstantial evidence of RES being a new beneficial molecule to disrupt tumor progression and metastasis upon resolving its hydrophobicity- and low solubility-related drawbacks.

Combining RES induces tumor cell death

Several previous studies investigated the role of RES in sensitizing tumor cells to conventional chemotherapy (Jie et al. 2019; Mahmoud et al. 2019). Most studies indicated that RES induced apoptosis commonly through the intrinsic apoptotic pathway, involving a diverse array of non-receptor-mediated stimuli producing intracellular signals that were mitochondrial-initiated events (Elmore 2007).

Several studies applied a combination of RES with antitumor antibiotics and microorganism-derived antineoplastic drugs. Here, we describe examples of RES combined with chemotherapeutic drugs.

*Doxorubicin: Combination studies of doxorubicin (DOX), also called Adriamycin, a hydroxy derivative of daunorubicin obtained from *Streptomyces peucetius*, yielded interesting results.

Doxorubicin, an antineoplastic agent, affects cancer cells through DNA intercalation, resulting in the disruption of Topoisomerase II (Top2) and the generation of reactive oxygen species (ROS), leading to cell membrane and mitochondrial membrane damage (Fatease et al. 2019). This drug has limited efficacy in colorectal cancer due to multidrug resistance. Therefore, it was combined with RES polyphenols (RES) and didox (DID) (Khaleel et al. 2016). The results revealed an increase in p53 and Bax gene expression. The combination of DOX with RES significantly increased the expression of the Bax gene in HCT 116 cells. Similarly, the synergistic effect of the combined DOX and RES tested on breast cancer cell lines MCF-7 and MDA-MB-231 chemosensitized doxorubicin through apoptosis increased (BAX: BCL-2 ratio and Caspase-9) (Kim et al. 2014; Rai et al. 2016).

These polyphenol agents reinforced the chemotherapeutic function of DOX. Indeed, the mechanism is thought to involve an apoptosis marker increase.

Other combination studies investigated the association of RES with rapamycin in papillary thyroid cancer cell lines (KTC-1 and TPC-1 cell lines) (Bian et al. 2020), statistically significantly increasing the proportion of G0/G1 cells and the number of apoptotic cells and also inducing the expression of apoptotic proteins caspase-3,-8,9, and Bax compared to cells treated with a single compound.

*Cisplatin: The combination treatment of cisplatin and RES (CDDP/RSV) synergistically induces apoptosis by increasing the percentage of apoptotic cells following Annexin V-PE binding and the cleavage of caspase-3 and PARP (Lee et al. 2016). Moreover, CDDP/RSV

increased ROS production and mitochondrial membrane potential depolarization with an increased BAX/BCL-2 ratio (Lee et al. 2016). These changes suggest CDDP/RSV-induced apoptosis. Furthermore, Hernandez-Valencia et al. (2018) reported that RES-induced sensitivity to CDDP in MCF-7 and MCF-7R cells regulates p53 protein expression (Hernandez-Valencia et al. 2018).

Li and collaborators demonstrated that RES promoted pulmonary H446 cell line inhibition by cisplatin, supported by mitochondrial depolarization through cytochrome c release from the mitochondrial compartment to the cytoplasm, apoptosis-inducing factor translocation from the mitochondrial compartment to the nucleus, and altered Bcl-2, Bcl-xL, and Bax protein levels (Li et al. 2018).

*Etoposide (VP-16): A topoisomerase II inhibitor and effective anticancer drug demonstrating powerful apoptotic effects when combined with RES on Merkel cell carcinoma (Heiduschka et al. 2014).

*Melphalan: Combined RES with Melphalan (MEL) application on the MCF-7 and MDA-MB-231 breast cancer cell lines indicated that RES could sensitize MCF-7 cells to MEL-induced apoptosis by involving p53 level enhancement, procaspase 8 reduction, and caspase 7 and 9 activation (Casanova et al. 2012).

*Paclitaxel: Acyclodecane (PAX) isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, a group of plant alkaloids, and natural products modify regulatory protein expression when combined with RES and synergistically increase apoptotic activity (Jazirehi and Bonavida 2004). Interestingly, markers for apoptosis, mitochondrial membrane depolarization and mitochondrial function, intracellular steady-state ROS levels, caspase 3 activity, TRPM2 current density, and Ca2+ fluorescence intensity significantly increased in DBTRG glioblastoma cells following the treatment with PAX and RES (Öztürk et al. 2019).

*5-Fluorouracil (5-FU): A common chemotherapeutic agent that belongs to the group of anti-metabolites interfering with DNA synthesis by blocking the thymidylate synthetase conversion of deoxyuridylic acid into thymidylic acid. This agent is used for CRC treatment, indicating high and inadequate response rates. RES reportedly induces a significant apoptosis increase (caspase-3) and potentiates the effects of 5-FU through the suppression of TNF-β expression in malignant human CRC cell lines (HCT116) and their corresponding isogenic 5-FU-chemoresistant-derived clones (HCT116R) in a 3D-alginate tumor microenvironment (Buhrmann et al. 2015; Buhrmann et al. 2018). Interestingly, treating cholangiocarcinoma cell lines with RES before 5-FU, gemcitabine, or mitomycin C supplementation increased apoptosis with higher efficiency compared to treatment with single chemotherapeutic agents (Frampton et al. 2010).

*Clofarabine: RES combined with clofarabine, an adenine arabinonucleoside derivative acting as an antineoplastic antimetabolite, induced Mcl-1 protein level down-regulation in MSTO-211H malignant mesothelioma cell lines, potentially exhibiting apoptotic activity (Lee et al. 2014; Lee et al. 2015). Elsewhere, RES cooperates with other chemical drugs, like intracellular protein inhibitors, to overcome chemotherapeutic resistance. RES combined with BRAFinhibitor, targeting BRAF-V600E/K mutated kinase (a driver mutation in 50% of cutaneous melanoma), dramatically reduced BRAF-resistant cutaneous melanoma cell numbers (Corre et al. 2018).

Combining RES improves tumor cell antiproliferation

RES causes improved growth inhibition of several tumor types, such as colon, breast, pancreas, prostate, ovarian, and endometrial cancers, as well as lymphomas (Neves et al. 2012). Several studies have revealed the antiproliferative potential of RES combined with chemotherapeutic drugs. Its synergistic effect with DOX on MCF-7 and MDA-MB-231 breast cancer cell lines inhibited breast cancer cell proliferation and invasion by reducing breast cancer cell wound healing and clonogenic potentials (Kim et al. 2014; Rai et al. 2016). RES was recently proven to inhibit renal cell carcinoma growth by inhibiting the PI3K/AKT pathway in paclitaxel-resistant cells (Jie et al. 2019).

In addition, Buhrmann and collaborators reported the antiproliferative effect of RES against colorectal CRC by promoting the invasion inhibitory effects of 5-FU (Buhrmann et al. 2015). Cholangiocarcinoma cell lines treated with the combination of RES with 5-FU, gemcitabine, or mitomycin C showed massively reduced cell proliferation compared with those treated with single chemotherapeutic agents (Frampton et al. 2010). Furthermore, Zhou and collaborators demonstrated that RES combined with gemcitabine tested on pancreatic cancer cell lines suppressed SREBP1 (sterol regulatory element-binding protein 1) proliferation, reversed the gemcitabine-induced stemness, and interestingly suppressed cancer cell proliferation, invasion, and migration (Zhou et al. 2019). Similarly, RES inhibited XRCC1 (X-ray Repair Cross-Complement Group 1 Protein) expression and enhanced the etoposide-induced cell death and antiproliferation effect in human non-small-cell lung carcinoma cells.

Clinical trials using RES with anticancer drugs

Most cancer drugs are derived from natural sources such as plants and bacteria, whereas others come from synthetic or semisynthetic processes (Gielecińska et al. 2023). These agents have been used due to their efficacy in fighting cancer. However, their clinical limitations include multidrug resistance and several side effects such as nausea, vomiting, loss of appetite, diarrhea, skin rash, hair loss, tiredness, dizziness, blurred vision, insomnia, and headache. Therefore, improving their efficacy and reducing their toxicity is becoming a trend, accomplished and investigated through cancer drug and RES combination. Several clinical trials have aimed to evaluate the impact of RES on signaling pathways involved in cancer development. Others assessed multiple signaling protein expressions that are important in cancer cell metabolism or quantified hormones in response to RES treatment. Further outcomes evaluated how RES influenced decreasing cancer cell growth and proliferation by investigating cancer cell growth- and survival-regulating gene and protein expression and by studying cross-sectional imaging and tumor markers. Heterogeneity between clinical trials investigated in this study might be due to differences in methodological factors (Table 3). Certain clinical trials quantified dietary polyphenols and methylxanthines in healthy and malignant mammary tissues from patients with breast cancer using chromatographic methods. Other preliminary studies determined RES pharmacodynamics, micronized RES (SRT501) safety, and tolerability in the analysis of the pharmacokinetic profiles in the blood, as well as healthy and malignant metastatic tissues.

Conclusion

Resveratrol, which is a natural phytoalexin, contains a wide range of biological properties, including antioxidant, anti-inflammatory, cardioprotective, and anti-tumor actions (Kursvietiene et al. 2016). Both the ability to

Table 3. Clinical trials using RES with anticancer drugs.

NCT Identifier (Reference)	Status	Year	Targeted cancer	Phase	Intervention/ treatment	Country
NCT00256334	Completed	2005	Colon Cancer	1	Resveratrol	United States of America
NCT00433576	Completed	2007	colorectal cancer	1	Drug: resveratrol Other: pharmacological study Other: laboratory biomarker analysis	United States of America
NCT00098969	Completed	2004	Unspecified Adult Solid cancer	1	resveratrol	United States of America
NCT00920803	Completed	2009	Colorectal Cancer and Hepatic Metastases	1	SRT501*	United Kingdom
NCT00455416	Recruiting	2007	Follicular Lymphoma	2	Omega 3 fatty acids (EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)) Selenium (L-Selenomethionine), Garlic extract (Allicin) Pomegranate juice (ellagic acid) Grape juice (resveratrol, quercetin) Green Tea (Epigallocathechin gallate)	Norway
NCT01107665	Completed		Melanoma	2	Pazopanib and Paclitaxel	United States of America
NCT00920556	Terminated (Study terminated.24 subjects enrolled;provided adequate data for decision making.)	2019	Multiple Myeloma	2	SRT501 Bortezomib	Denmark United Kingdom
NCT01476592	Completed	2011	Neuroendocrine cancer	Not Applicable	Resveratrol	United States of America
NCT04266353	Suspended (Due to COVID-19)	2020	Breast cancer	Not Applicable	Resveratrol (RSV)	United States of America
NCT03482401	Completed	2018	Breast Cancer	Not Applicable	Polyphenol	Spain

*a micronized oral formulation.

overcome multidrug resistance (MDR) and the ability to sensitize cancer cells to chemotherapeutic medicines have been proved successfully by it. To improve the anticancer activity, bioavailability, and pharmacokinetic profile of chemotherapeutics when coupled with RES, several different carriers have been created. *In vivo* and *in vitro* investigations, as well as clinical trials, have been conducted to investigate the impact that RES has on carcinogenic phases. Increasing the solubility of RES, altering administration methods, avoiding metabolism, and inventing new nanoformulations are some of the many studies that have been conducted with the intention of increasing RES levels. Despite this, there are still not many studies conducted on humans in this setting, which calls for additional research. In addition, there is a requirement for additional study that is more in-depth to discover efficient methods of employing RES for the prevention of cancer.

Considering this, it is necessary to conduct additional clinical trials to study the consequences of RES in conjunction with pharmacological medications.

Author contributions

IBY, OB, MJ, MAR, and NB wrote the drafts and guided the development of the article. IZ and AHH developed the strategy for the literature search, reviewed the outputs of the search, and reviewed and approved the manuscript.

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