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Review Article

Molecular Docking of Resveratrol with Ovarian Cancer-associated Proteins and Its Therapeutic Benefits

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Abstract

Ovarian cancer (OC) is a major global health problem. The main treatments are surgery and chemoradiotherapy. A drawback of the latter is that repeated treatments are likely to lead to cancer cells developing resistance to the drug, resulting in recurrence, development of metastases, and poor prognosis for patients. Consequently, there is interest in combining chemoradiotherapy with treatment using active components extracted from natural products. One such component is resveratrol (RVT), which is a natural anti-tumor ingredient extracted from plants. Although there are many reviews on the biological activity of RVT, only a few studies have been performed to investigate the diversity of protein binding of RVT with OC and the application of various novel drug formulations containing RVT to treat OC. The review presented here may provide some ideas for the prevention and treatment of OC.

Introduction

Ovarian cancer (OC) has been described as a "silent killer". Onset is often hidden, and in many patients the disease has reached an advanced stage by the time it is discovered.[1] In 2024, the annual incidence rate of OC was estimated to be approximately 11.2 cases per 100,000 individuals, while the mortality rate was approximately 7.6 cases per 100,000 individuals.[2]

There are two main histological subtypes of OC, namely epithelial OC and non-epithelial OC. Epithelial OC is the most common subtype and includes serous OC, mucinous OC, and clear cell carcinoma, and accounts for 90% of all cases.[2] OC does not always begin in the ovary, and in many cases begins in the fallopian tubes.[3] Especially due to the anatomical position of the ovary in the retroperitoneum, an effective screening strategy does not exist for detecting OC, and most cases are identified via breast cancer 1 or breast cancer 2 germline mutations or other limited genes associated with high risk of OC,[4] which is the main reason why many women have reached Stage III when they are diagnosed.[5]

After surgical resection of the OC lesion, radiotherapy and chemotherapy treatments are routinely given. Radiotherapy is a local treatment, the aim of which is to deliver as much radiation as possible to the tumor. However, because radiation has low selectivity for cells, to minimize damage to adjacent healthy cells, only body parts needing treatment are exposed to radiation. On the other hand, chemotherapy drugs target cancer cells in the human body by oral administration or injection, so that the whole body is exposed to anti-cancer drugs. Unfortunately, cancer cells typically become resistant to chemotherapeutic drugs such as paclitaxel and platinum compounds,[6] and the efficacy of chemotherapy is usually not satisfactory in the later stages of the disease.[7] The poor prognosis of patients and the decline in overall survival rate are major unsolved clinical needs in the treatment of patients with OC.

Anti-cancer treatments developed from natural products are attracting significant attention because of their convenience to source and good safety. Resveratrol (RVT) is a potential natural anticancer treatment without toxicity or adverse effects and is of particular in-

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terest. If natural products can be used to improve the efficacy of radiotherapy and the efficacy and long-term potency of chemotherapy, this will be of major benefit for increasing survival times for patients.

RVT (3,4′,5-trihydroxy-trans-stilbene) is a natural compound that is found in many plants, such as grapes, peanuts, blueberries, etc. It has been shown to have an inhibitory effect on many types of cancer cells, including lung cancer,[8] prostate cancer,[9] OC,[10] and oral cancer.[11] The structure of RVT is based on 3,4′,5-trihydroxystilbene, known as stilbene, which consists of two phenolic rings connected by a styrene double bond and exists in both cis and trans forms, which are both functional.[12] Trans-RVT can undergo isomerization to cis-RVT when exposed to solar or artificial light or UV radiation.[13] The mechanism of action of RVT in the treatment of cancer has been described by Ren *et al*.,[14] among others, leading to new ideas for research. RVT has both immunomodulatory and anticancer properties. In particular, its antioxidant activity and ability to inhibit enzymes may contribute to anti-inflammatory properties. Furthermore, studies have shown that RVT can stimulate autophagy and activate molecules related to vascular protection, induce the expression of KLF transcription factor 4 and NaVβ3, and subsequently activate signaling pathways associated with endothelial cells, thereby contributing to vascular protection.[15] By interfering with signaling pathways associated with cellular microenvironment components such as macrophages and fibroblasts, RVT can also enhance its anti-tumor effect.[16] RVT can also act as a nuclear transcription factor-κB (NF-κB) antagonist, inhibiting RANKL-induced NF-κB signaling, thereby reducing NF-κB activity. It modulates a specific gene expression profile, suppresses excessive tumor proliferation, and consequently diminishes or eliminates apoptosis resistance.[17]

In this review, the latest developments in using RVT to treat OC will be presented, with particular focus on its role in augmenting radiotherapy and chemotherapy treatments. The application of RVT to treat OC has been expanded by the use of a variety of encapsulated forms of delivery, and it is expected that RVT will have a broad range of applications in the future.

Structural properties of RVT and its binding to OC-related target proteins

RVT (3,4′,5-trihydroxy-trans-stilbene) is a compound with a non-flavonoid polyphenol structure, as shown in Figure 1. Near-plane trans-R forms a conjugate network with relatively poor rigidity and flexibility, and non-plane cis-R forms a more flexible structure that allows different interactions. Energy decomposition analysis has shown that trans-R is more potent than cis-R, and so the trans isomer is the most widely studied chemical form.[18] Important for cancer treatment, the hydroxyl position of polyphenols has an important influence on its interaction with enzymes, antioxidant activity, stability, and enzyme activity,[19] because phenolic hydroxyl groups easily interact with amino acid residues of target proteins *in vivo* through hydrogen bonds, hydrophobic interactions, electrostatic interactions, π-π superposition, and cation-π interactions.[20–22] The complementarity of these local structures means that the RVT-target interaction and binding are highly specific, which is important for targeting in anti-cancer treatments. We searched the PubMed, ScienceDirect, Google Scholar, Scopus, ISI Web of Science, ProQuest, and Embase databases from 2001 to 2025 using relevant keywords, including but not limited to "ovarian cancer signaling pathways", "resveratrol target proteins", "resveratrol AND ovarian cancer)", "sirtuin 1 (SIRT1) ovarian cancer", "estrogen receptor alpha (ERα) resveratrol binding", "peroxisome proliferator-activated receptor (PPAR-γ) ovarian cancer", and "phospholipase A2 (PLA2) resveratrol". The selection process employed strict inclusion criteria requiring targets to have both demonstrated relevance to OC progression and available structural data in the PDB (https://www.rcsb.org/). Through this approach, we identified several key targets involved in OC. Further analysis was conducted subsequently. The selection of PDB entries was based on stringent criteria, prioritizing structures with high resolution (typically < 2.5 Å), determined by X-ray crystallography, and preferably in complex with a relevant substrate or inhibitor to ensure the biological relevance of the active-site conformation, since consideration of the crystal structure is the most helpful way of understanding the binding pattern at the atomic level. Using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), the 3D structure of RVT was downloaded as the ligand.[23] Protein structures were prepared for docking using the protein preparation workflow via AutoDock Vina 1.1.2. This involved the addition of hydrogen atoms, assignment of partial charges, and removal of native ligands and water molecules. Crucially, the protonation states of key ionizable residues (e.g., aspartic acid, glutamic acid, and histidine) were carefully evaluated and adjusted to their most probable states at physiological pH to ensure an accurate representation of the binding interface.

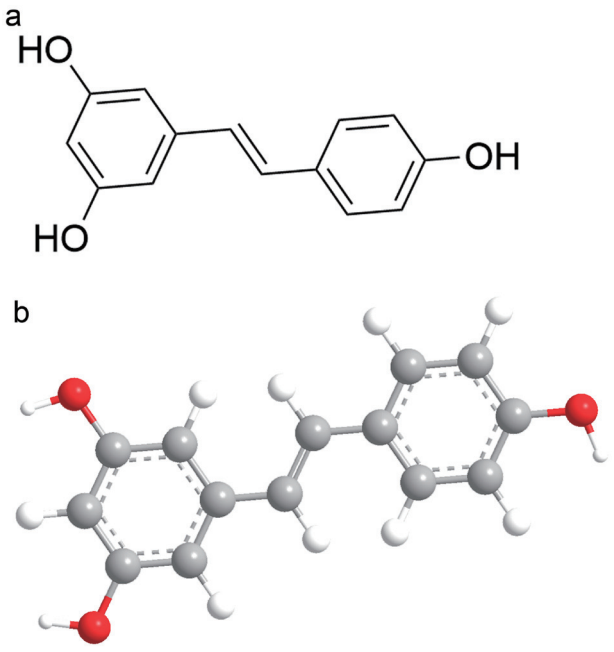

Fig. 1. Structure of RVT. (a) 2D structure of RVT; (b) 3D structure of RVT. RVT, resveratrol.

The docking calculations were carried out using AutoDock Vina, which employed a rapid grid-based method for energy evaluation and an efficient algorithm for searching the conformational space of the ligand. The search space (grid box) was explicitly defined to encompass the known active site of each target protein. The resulting docking poses were clustered and ranked based on their calculated binding affinity (kcal/mol).

The predicted binding energies for RVT against each protein target are summarized in Table 1, and the molecular docking diagrams are provided in Figure 2.

Binding of RVT to SIRT 1 protein (PDB ID:5BTR)

SIRT1 functions as an NAD^+-dependent deacetylase, exerting its

Table 1. Molecular docking results of RVT with target proteins

Target protein	PDB ID	Binding energy	Binding affinity
SIRT1	5BTR	**−8.3**	Strong
PLA2	4QER	**−6.9**	Strong
E2	4PP6	**−7.8**	Strong
PPAR-γ	4JAZ	**−8.0**	Strong

Binding energy < −5.0 kJ/mol indicates strong binding ability (highlighted in bold). PDB, Protein Data Bank; PLA2, phospholipase A2; PPAR-γ, peroxisome proliferator-activated receptor gamma; RVT, resveratrol; SIRT, sirtuin 1.

regulatory influence through deacetylation of downstream proteins. It can delay cell aging, helping cells resist external stress and improving metabolism.[24] The expression of SIRT1 has been shown to be elevated in mammalian follicles, where it is capable of modulating oestrogenic function.[25] SIRT1 also controls the secretion of tumor-promoting exosomes during cancer invasion and is overexpressed in patients with OC.[26] RVT is a polyphenol compound that can stimulate SIRT1 production.[27] A positive correlation between SIRT1 expression level and overall survival in OC has been reported.[28] Furthermore, it is predicted that RVT stimulates SIRT1 expression in follicular cells.[29] The combination of melatonin and RVT has been demonstrated to exert a neuroprotective effect against amyloid-related toxicity by stimulating SIRT1 activity.[30] Studies *in vivo* and *in vitro* show that SIRT1 is a potential target for treating diseases.[31,32] Besides the catalytic domain of SIRT1, RVT also requires the presence of the N-terminal domain, which forms hydrogen bonds with Asp298 through the hydroquinone ring and hydrophobic interactions with the Gln294 receptor residue, while the 4-hydroxyphenyl ring forms an important hydrogen bond with Lys444 and a hydrophobic bond with Thr209 of the receptor molecule.[33] It can be posited that the formation of these bonds may provide molecular modeling data for RVT-stimulated SIRT1 expression elevation.

Binding of RVT to PLA2 protein (PDB ID:4QER)

PLA2 is a hydrolase that can catalyze the 2-acyl group on a phospholipid glycerol molecule and is also a rate-limiting enzyme involved in the production of bioactive substances such as arachidonic acid, prostaglandin, and platelet-activating factor. The lipid medium produced plays a key role in membrane channel activation, information transmission, hemodynamics, and pathophysiology during inflammation and tissue injury, as well as in regulating metabolism inside and outside cells.[34] The PLA2 superfamily comprises a series of hydrolases that facilitate the release of membrane fatty acids, resulting in the production of arachidonic acid and lysophospholipids. This process culminates in the generation of biologically active lipid signaling molecules. The PLA2 enzyme plays an important role in OC in the downregulation of phosphatidylethanolamine and ether phosphatidylcholine, and as a rate-limiting enzyme in phospholipid hydrolysis, it exhibits specific chronic inflammation and disturbances in homeostasis, thus making it a potential target for cancer therapeutic drug development. Inhibition of iPLA2β to impede ovarian carcinogenesis may represent a future direction for lipid metabolism regulation in cancer therapy.[35] RVT has been demonstrated to induce changes in the membrane morphology of HepG2 cells, which is concomitant with a decline in PLA2G2 expression.[36] PLA2 is expressed in OC effusion,[37] and studies have shown that targeting lipogenesis with the metabolic inhibitor PFK158 attenuates the expression of PLA2 subtypes in an autophagy-dependent manner, which can offset the progression of OC and suggests that great potential exists for using targeted phospholipases in the treatment of OC.[38] RVT affects the structure and stability of the PLA2 enzyme through hydrophobic and electrostatic interactions.[39] In the structure of RVT, due to the action of hydroxyl groups, the 4-hydroxystyryl moiety with relatively low polarity is wrapped in the buried environment of the substrate-binding gap, and the hydroxyl groups generate hydrogen bond interactions with multiple amino acid residues, while

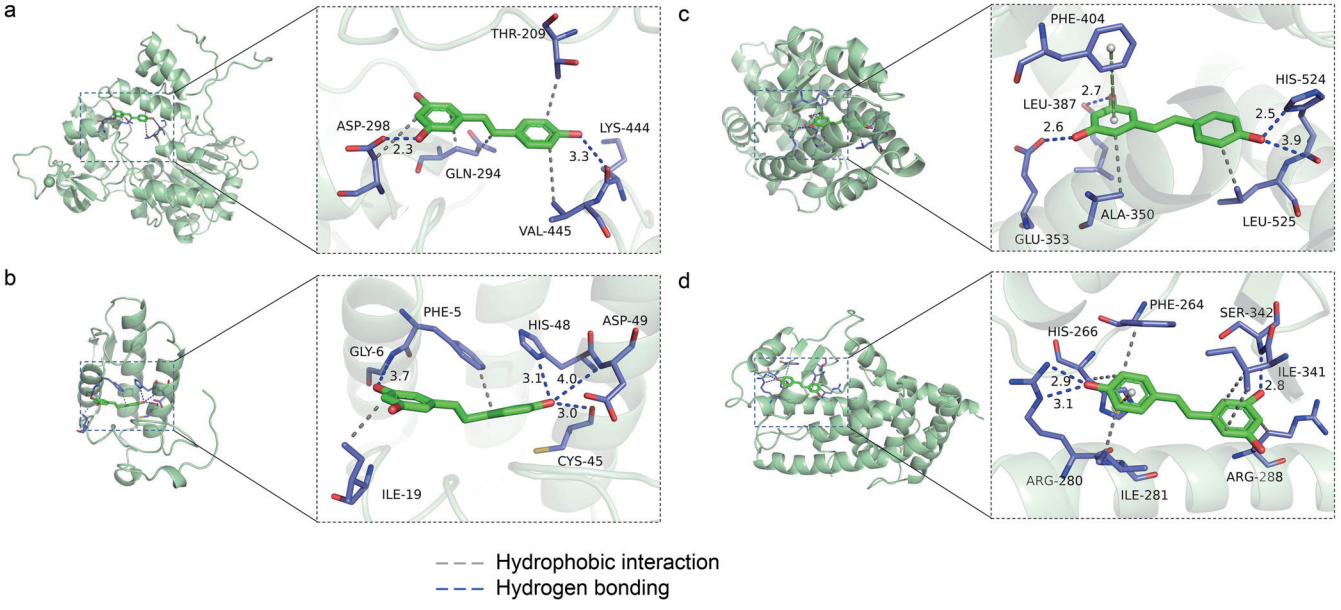

Fig. 2. Binding of RVT to high-expression proteins in ovarian tumors. (a) Binding of RVT to SIRT1 protein; (b) Binding of RVT to PLA2 protein; (c) Binding of RVT to E2 protein; (d) Binding of RVT to PPAR-γ protein. PLA2, phospholipase A2; PPAR-γ, peroxisome proliferator-activated receptor gamma; RVT, resveratrol; SIRT1, sirtuin 1.

the m-hydroquinone ring with relatively strong electronegativity is close to the surface of PLA2. Two important hydrophobic interactions are formed between RVT and nearby Ile19 and Phe5, and all RVT-binding residues are cyclic or alpha-helical.[40] The existence of these chemical bonds indicates that RVT can bind closely to the highly expressed proteins in the development of OC after entering the body, and these proteins may become target proteins for the treatment of OC in the future.

Binding of RVT to E2 (estrogen protein, PDB ID:4PP6)

The estrogen receptor alpha (E2) protein is highly expressed in epithelial OC and is associated with poor prognosis in patients with OC.[41] A large-scale study that included 2,933 patients with OC found that in the high-grade serous, low-grade serous, and endometrioid subtypes of epithelial OC, the expression of estrogen receptor alpha was significantly higher than that in the other subtypes. The positive rates of E2 (nuclear staining ≥ 50%) were 60%, 71%, and 60%, respectively.[42] In particular, E2 stimulation enhances the influx of Ca^{2+} and promotes the proliferation and invasion of OC cells.[43] E2 promotes the proliferation of epithelial ovarian cancer cells by upregulating genes related to proliferation, such as c-fos and c-myc. Furthermore, it can promote the migration and epithelial-mesenchymal transition of epithelial ovarian cancer cells by reducing the expression of E-cadherin and increasing the expression of Snail and Slug.[44] RVT has a weak estrogen-like effect, which allows it to bind to estrogen receptors and exert a biological effect similar to estrogen.[45] A simulation using molecular dynamics showed that RVT is a selective estrogen receptor modulator, and its actual effect is highly dependent on the cellular environment and whether co-regulatory proteins are present.[46] The m-hydroquinone moiety present in RVT and Phe404 can form a π–π conjugated structure, enabling RVT to more easily enter the cavity of the estrogen protein and form hydrogen bonds with Glu353 and Leu387, while the 4-hydroxystyryl group with relatively low electronegativity can interact with His524.

Binding of RVT to PPAR-γ protein (PDB ID:4JAZ)

PPAR-γ is a ligand-activated transcription factor. There are three isoforms of human PPAR, namely PPAR-α, PPAR-β/δ, and PPAR-γ, and PPAR-γ is the most widely studied subtype. PPAR-γ consists of 11 to 13 α-helices sandwiched between three layers of antiparallel helices and a four-stranded β-sheet that folds into a large hydrophobic cavity, which facilitates the binding of ligands to receptors, and is expressed in a large number of epithelial ovarian tumors and cell lines.[47,48] PPAR-γ is a key factor in macrophage differentiation and interacts with CCAAT/enhancer-binding protein β, a transcription factor essential for activating the immune system. This implies that PPAR-γ may serve as a potential therapeutic target for OC.[49] In the later stage of OC treatment, cisplatin can increase the content of PPAR-γ in ovarian tissue and enhance ovarian toxicity.[50] RVT activates PPAR-γ, which in turn inhibits the expression of Cyclin D1, causing cancer cells to arrest in the G1 phase and reducing their ability to divide.[51] We modeled the specific binding site using molecular docking to demonstrate that RVT is bound to the deep cavity of one of the monomeric units of the PPAR-γ dimer structure, rather than to its surface.[52] Thus, the stilbene moiety has unique conjugated structural characteristics, whereby the 4-hydroxyphenyl ring forms a hydrophobic interaction with Phe264 and Ile281, and the hydrogen bond energy between the m-hydroquinone ring and Ser342 causes partial displacement of some residues in the PPAR-γ domain and tight binding with RVT.

The specific roles of RVT in the treatment of OC

Anti-inflammatory

Most often, it is chronic inflammation that is the intrinsic driving force behind the transformation of precancerous lesions into malignant tumors.[53,54] In particular, abnormal secretion and expression of inflammatory factors are key to tumorigenesis.[55] Lipopolysaccharide (LPS), the basic glycolipid component of Gram-negative bacterial endotoxin, can cause inflammatory reactions in the host.[56] It can reduce inflammation by inhibiting the production and release of the pro-inflammatory cytokine interleukin (IL)-1β and pyroptosis (an inflammatory form of cell death) in macrophages.[57] RVT has the potential to reduce the expression of such inflammatory mediators, including prostaglandin E2 and BV-2, or monocyte LPS-stimulated monocyte chemoattractant protein-1.[58,59] In addition, LPS-stimulated expression of toll-like receptor 4 was decreased after RVT pretreatment.[60] RVT could inhibit the expression of inducible nitric oxide synthase and IL-6 in LPS-treated RAW264.7 cells in a dose-dependent manner.[61] IL is a member of the classical inflammatory factor family, and remarkably higher levels of IL-6 and vascular endothelial growth factor-A were reported in ascites of patients with epithelial OC compared with a control group.[62] Possibly, RVT could inhibit the migration of OC cells induced by the pro-inflammatory factor IL-6 and regulate autophagy,[63] and thus control the inflammatory lesions of ovarian tumors by inhibiting inflammatory factors. Furthermore, the ubiquitous nuclear transcription factor NF-κB can regulate the expression of many inflammatory response regulatory genes, and activation of the NF-κB pathway can lead to LPS-stimulated expression of inflammatory cytokines such as IL-1, IL-6, IL-10, and tumor necrosis factor.[64] In addition, the ability of RVT to down-regulate NF-κB activation in macrophages is higher than that of naringenin and naringin.[65] RVT demonstrated an anti-inflammatory effect via SIRT-1 activation,[66] and the binding of RVT to SIRT-1 enhanced its attachment to a RelA/p65 substrate,[67] thereby activating leukocyte and pro-inflammatory cytokine pathways.[68]

Antioxidation

Oxidative stress is defined as a relative excess of reactive oxygen species (ROS) and typically accompanies excessive proliferation of tumor cells.[69] In particular, persistent oxidative stress can cause DNA damage and gene mutation, leading to irreversible imbalance of ROS in the body and occurrence of OC.[70] ROS play a significant role in platinum resistance in OC by activating various cellular pathways and targets. ROS can both promote and inhibit cell death, creating a complex interplay in response to platinum-based chemotherapy.[71] RVT extracted from plants such as grapes is a natural antioxidant and has been shown to play a significant role in antioxidant activity,[72] with structurally related hydroxyl groups involved in mechanisms that reduce ROS and free radicals as well as increase endogenous antioxidant biosynthesis. RVT can kill OC stem cells by up-regulating ROS levels in cells, and ROS can damage the self-renewal ability of OC stem cells surviving RVT treatment.[73] Ibrahim *et al*.[74] demonstrated that RVT had a potential protective effect on cisplatin-induced ovarian and uterine toxicity in female rats, mainly by reducing oxidative stress, inflammation, and apoptosis to inhibit cisplatin-induced toxicity.High-valent selenium nanodrugs loaded with RVT can stimulate ROS overproduction, which significantly induces mitochondrial dysfunction and promotes caspase-activated cell apoptosis and migration, and inhibits OC development.[75] RVT exerts its antioxidant properties mainly through a variety of signaling pathways that activate antioxidant enzymes.[76]

Antiproliferation and cell cycle arrest

The regulatory mechanism of the cell cycle mainly depends upon compounds such as cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors,[77] and uncontrolled proliferation of cancer cells is largely due to the abnormal activity of cyclins.[78] Gene expression analysis using three different types of cell lines and clinical samples found that cyclin A1 was persistently overexpressed in recurrent and drug-resistant ovaries, and suggested that cell cycle inhibitors may be potential drugs for the treatment of cancer. RVT down-regulated the phosphorylation of protein kinase B (AKT) and GSK-3β at Ser9 in a concentration-dependent manner and reduced extracellular signal-regulated kinase 1/2 in OC cells, thereby inhibiting the expression of cyclin D1.[79] Derivatives of RVT enhance the effectiveness of cisplatin in treating OC by improving its ability to reduce cell viability, inducing apoptosis, as well as arresting the cell cycle, leading to a greater proportion of cells in the sub-G1 phase.[80] RVT induces both cell cycle arrest and apoptosis in ovarian adenocarcinoma SKOV-3 cells by activating the p38 mitogen-activated protein kinase pathway and inhibiting the AKT pathway.[81] Zhong *et al*.[82] studied the inhibitory effect of RVT on OC cells using two human OC cell lines, OVCAR-3 and CAOV-3, and found that RVT-treated human OC cells had significant accumulation in the G1 phase and an increased apoptosis fraction, and were significantly blocked in the S phase. G2/M phase block played a significant role in enhancing the sensitivity of OC cells to immunotherapy.[83] RVT could not only inhibit the growth of OC but also play a role in drug-resistant OC.

In the structure of RVT, the presence of 4′-OH and stereoisomers in the trans isomer (4-hydroxystyryl moiety) is necessary to inhibit cell proliferation.[84] In particular, RVT was able to inhibit the proliferation of SKOV-3 cells by inhibiting the glycolysis-targeted AMPK/mTOR pathway and inhibit the growth of OC and liver metastasis in xenograft mouse models *in vivo*.[85] Prostaglandins are the products of cyclooxygenase (COX-2) acting on arachidonic acid and have been shown to stimulate cell proliferation, promote angiogenesis, and inhibit apoptosis in cancer.[86,87] RVT can inhibit the progression of tumors by directly blocking COX-2 activity.[88] It has also been reported that RVT has another key effect on COX-2 in OC cells, namely induction of anti-proliferation of tumor cells by activating extracellular signal-regulated kinase 1/2-dependent COX-2 nuclear accumulation and p53-dependent apoptosis activation/phosphorylation.[89] The specific possible mechanisms of RVT in OC are shown in Figure 3.

Regulation of autophagy in OC cells

Autophagy is an evolutionarily conserved catabolic process in mammalian cells that participates in the regulation of cellular homeostasis by engulfing endogenous (e.g., organelles) and exogenous (e.g., pathogens) materials to form double-membrane autophagosomes and degrading these substrates after fusion of the autophagosome with the lysosome.[90] Tumor cells rely more on autophagy for survival than normal cells.

Autophagy has a two-sided role in tumor cells, as shown in Figure 4. On the one hand, autophagy can prevent chronic tissue damage and inhibit the accumulation of oncogenic protein aggregates by controlling organelles in the early stage of tumor formation, thereby achieving the effects of inhibiting tumor growth, interfering with tumor occurrence, and maintaining the stability of the microenvironment.[91,92] On the other hand, autophagy at the advanced stage of tumor development can serve as a mechanism for cell survival, protection, and defense, maintaining mitochondrial function in cancer cells and enhancing cellular stress capacity, thereby maintaining tumor metabolism, promoting tumor growth, and increasing tumor formation, leading to tumor resistance.[73,93,94] Autophagy thus contributes to macromolecular renewal, cell homeostasis, and survival, and represents a pathway that can be used for anticancer therapy,[95] as shown in Figure 4. The potential role of autophagy in tumors is complex and relevant to both tumor induction and inhibition.

Autophagy is essential for quiescent OC spherical cells to re-enter the cell cycle.[96] LC3 has been best investigated and characterized as an autophagosome marker in mammalian cells.[97] Autophagy was found to be enhanced with Beclin-1 upregulation and LC3 enzymatic cleavage in RVT-treated OC cells.[98] In particular, RVT was able to recover from autophagy and promote apoptosis by inhibiting the Hh pathway in response to the effects of platinum chemotherapy drugs on OC cells.[99] The combination of RVT and cisplatin could reduce the phosphorylation level of AKT and thus induce autophagy.[100] In other studies, it has been shown that RVT can significantly induce autophagy and promote apoptosis of OC cells.[101] Autophagy is a mechanism of RVT in regulating the microenvironment of OC.[102] Although RVT-induced cell death can trigger apoptosis (another pathway of cell death), autophagy is also activated, and gene products regulating autophagy can play the role of tumor suppressor genes. Studies carried out in this laboratory have shown that RVT can inhibit the proliferation of OC cells by regulating autophagy (see Fig. 3 for more details on the roles and targets of RVT).

Application of new preparations of RVT in OC

Application of novel preparations in targeted OC

Although the therapeutic effect of RVT on OC is supported by many *in vitro* experiments,[103,104] poor bioavailability and water solubility hinder the development of studies to investigate the clinical efficacy of RVT. Epithelial OC cannot be accurately diagnosed by imaging techniques such as magnetic resonance imaging (MRI).[105] Therefore, it is hoped that by constructing delivery systems that contain multiple components, they can not only target and treat the tumor with reduced toxic effects, but also support the development of new methods for early detection of OC lesions. Biomedical imaging can easily combine targeted cancer treatment,[106] electron modulation and energy conversion of the nanocatalyst under X-ray irradiation can greatly improve the efficiency of catalytic radiosensitization and further improve clinical curative effects,[107] and can also achieve therapeutic purposes by enhancing the permeability and retention effect and actively targeting accumulation in tumors. Intelligent response drug administration systems have been developed by constructing a gold nanodot–paclitaxel–polylysine (AuNDs-PTX-PLL) core-shell integrated diagnosis and treatment nanosystem, which not only solved the problem of poor water solubility and drug resistance of paclitaxel, but also enabled the nanogold particles to be used for real-time tracking and auxiliary diagnosis of tumors through multimodal imaging such as fluorescence and CT.[108] Previous studies have demonstrated that chitosan/PEG nanoparticle-embedded oleogels can significantly enhance the bioavailability and antioxidant capacity of RVT.[109] Novel nanoformulations for RVT delivery include polymer nanoparticles, liposomes, micelles, metal nanoparticles, and solid lipid nanoparticles. Imaging probes may be included in the nanoparticles, allowing the adverse effects of drugs to be predicted by providing data on potential non-target aggregation sites in healthy tissue.[110]

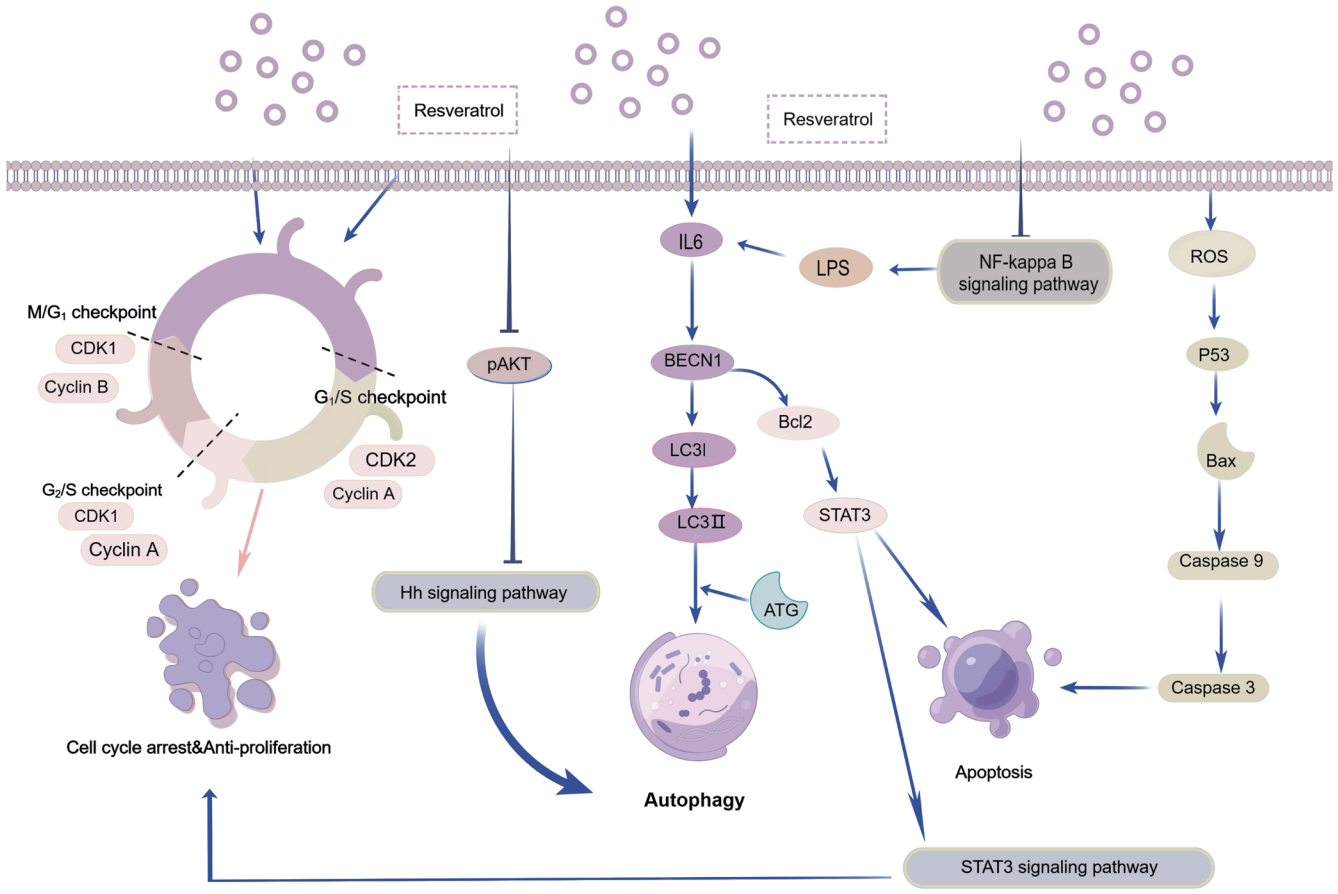

Fig. 3. Mechanisms of RVT in the treatment of OC, by Figdraw. ATG, autophagy-related gene/protein; Bax, Bcl2-associated X protein; Bcl2, B-cell lymphoma 2; BECN1, Beclin-1; CDK, cyclin-dependent kinase; IL6, interleukin-6; LC3I, microtubule-associated protein 1A/1B-light chain 3-I; LC3II, microtubule-associated protein 1A/1B-light chain 3-II; LPS, lipopolysaccharide; OC, ovarian cancer; P53, cellular tumor antigen P53; pAKT, phosphorylated protein kinase B; ROS, reactive oxygen species; RVT, resveratrol.

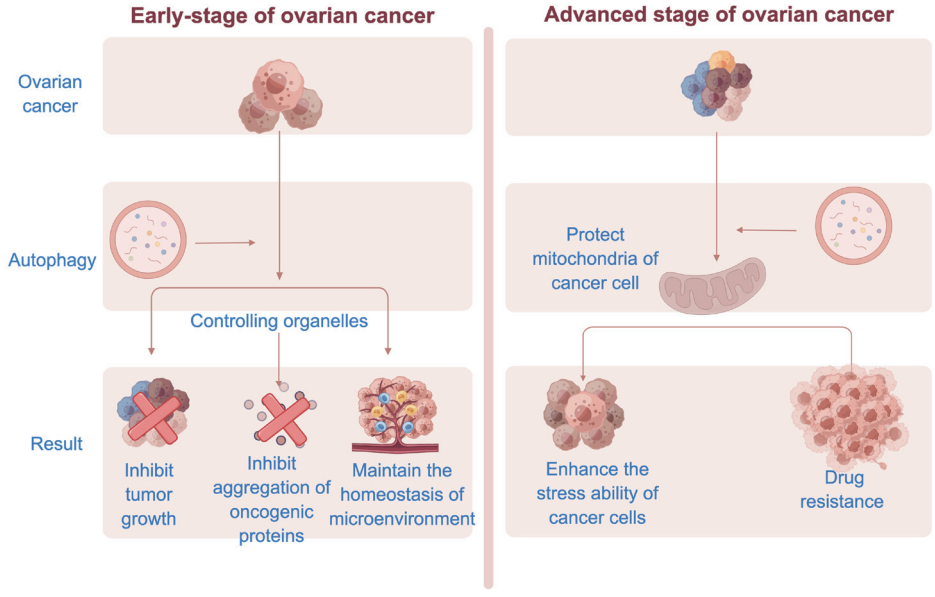

Fig. 4. Role of autophagy in tumors, by Figdraw.

Table 2. The current literature concerning the chemosensitizing effect of RVT combined with conventional anticancer drugs in OC

Class	Drug	Effect	Reference
Chemosensitization	RVT,docetaxel and doxorubicin	Inhibition of P-glycoprotein and down-regulation of MDR1 gene	108
	RVT, cisplatin and oxaliplatin	Sensitized the OC cells to platinum-induced apoptosis	112
	RVT and Cisplatin	Enhanced cisplatin toxicity to OC cells	113
	Sorafenib plus topotecan	Improved progression-free survival	117
radiosensitization	Radiotherapy and RVT[a]	a. increases the apoptosis and autophagy of tumor cells	125
		b. restored salivary amylase and SOD activity	126
		c. reduced radiation-induced chromosome aberration frequencies	127
		Associated with increased autophagy and apoptosis	128
		Enhanced radiation efficacy was achieved through the regenerative gene (REG) III expression pathway	129
		The treatment delayed repair of radiation-induced DNA double-strand breaks (DSBs) and prolonged G2/M phase arrest	130

[a]RVT can also be used as a radioprotective agent to reduce the adverse effects of radiation therapy, which in most people can cause dry mouth, mucositis, and dysphagia. a: Increase the apoptosis and autophagy of tumor cells, and reduce the volume and weight of tumors *in vivo*. b: RVT can reverse the radiation-induced decrease in salivary secretion and restore the activities of salivary amylase and SOD. c: RVT can reduce radiation-induced chromosome aberrations in mouse myeloma cells. The data in this table are all preclinical data. MDR1, multidrug resistance protein 1; OC, ovarian cancer; RVT, resveratrol; SOD, superoxide dismutase.

New dosage forms of RVT for the treatment of OC

Formulations containing RVT alone

Nanoconjugation can enhance the antioxidant properties of RVT. Compared with the free drug, the bioconjugated drug can improve effective drug loading and is more effective in killing cancer cells. Researchers synthesized RVT-loaded zinc oxide nanoparticles, and in the human OC cell line PA1, RSV-ZnO nanoconjugates could induce cell apoptosis by enhancing intracellular ROS levels and mitochondrial membrane depolarization. Moreover, RSV-ZnO nanoconjugates had a stronger anticancer effect than free RSV.[111] RVT-loaded bovine serum albumin nanoparticles induced apoptosis in SKOV-3 OC cells through the AIF apoptotic pathway, which was considered to be an alternative to the caspase-dependent apoptotic pathway.[112]

As a novel delivery system in the treatment of OC, arginine-glycine-aspartic acid-conjugated RVT human serum albumin nanoparticles showed a higher cell uptake rate and cell inhibition rate in a model of OC as compared with a control group, and demonstrated good tumor enrichment characteristics and significant tumor inhibition differences in an *in vivo* experiment.[113] The RVT-conjugated gold nanoparticle system exhibits remarkable efficacy in suppressing hydrogen peroxide-induced oxidative stress, including inhibition of ROS generation, reduction of malondialdehyde production, and prevention of glutathione depletion.[114] In addition, researchers have also developed RVT liposomes as a new therapeutic platform for magnetic resonance imaging-guided targeted therapy for Parkinson's disease.[115]

Combination with preparations loaded with RVT

Combining the treatment effects of different therapeutic drugs is an interesting topic in the field of OC treatment. This so-called combination therapy can reduce adverse effects and prevent the development of drug resistance. For example, co-administration of RVT and curcumin in a polymer micelle can reduce the cardiotoxicity of doxorubicin hydrochloride by reducing apoptosis and increases in ROS, while at the same time improving the efficacy of doxorubicin hydrochloride against OC cells.[116] Similarly, polymer micelle co-administration of quercetin/RVT and RVT/curcumin can enhance drug targeting. In particular, compared with using adriamycin alone, copolymerized micelles combined with adriamycin reduced tumor size and the extent of heart damage in mice,[117] and had the ability to promote apoptosis of OC cells. RVT- and curcumin-loaded core-shell nanoparticles demonstrated enhanced cellular uptake and significantly reduced viability in OC cells.[118] Researchers in this laboratory are developing nanoparticles loaded with RVT that will be used to guide targeted therapy for OC using MRI and other imaging techniques.

The sensitization effect of RVT on OC treatment

The immediate remission rate of advanced OC can reach more than 80% after receiving chemotherapy drugs. However, most patients relapse within two to three years, and almost all relapsed OC is resistant to chemotherapy,[119,120] which is the main reason for the high mortality rate of patients with advanced OC.[121] The combination of natural compounds and chemotherapy drugs may be able to produce additive/synergistic effects, improve drug activity, and reduce adverse effects (please see Table 2 for specific drugs and mechanisms of action).[108,112,113,117,122–130] The drug or combination drug system can be designed to have nano- or micron-scale dimensions and be released into tumors to affect the cellular microenvironment.[131] Research focusing on a phase-change material-gated Ti_3C_2Tx nanosheet as a photothermal-responsive drug delivery system for loading natural RVT has been conducted, with the goal of achieving synergistic radiosensitization in a precisely controlled manner. This system demonstrates remarkable capabilities. It significantly boosts the biophysical diffusion of RVT within physiological solutions, ensuring efficient delivery to target sites. Simultaneously, it substantially inhibits the enzymatic activity that is

Table 3. Various effects and molecular targets of RVT nanoformulations involved in OC

Drug class	Type of nano-based RVT	Effect	Reference
Individual delivery	RVT—ZnO nanohybrid	Mitochondrial membrane depolarization and ROS formation	93
	RVT-loaded bovine serum albumin nanoparticles	Apoptosis inducing factor (AIF) apoptosis pathway	94
	RGD-conjugated RVT human serum albumin nanoparticles	cell inhibition and tumor growth inhibition	95
	Gold Nanoparticles Encapsulated RVT	Inhibit ROS production, MDA generation, and GSH consumption	113
Co-delivery	Polymeric micellar co-delivery of RVT and curcumin	Apoptosis and ROS formation	97
	Combinational polymeric micelles co-delivery of quercetin/RVT and res-veratrol/curcumin	Induction of apoptosis	98

The data in this table are all preclinical data. GSH, glutathione; MDA, malondialdehyde; OC, ovarian cancer; RGD, arginine-glycine-aspartic acid; ROS, reactive oxygen species; RVT, resveratrol.

enhanced by radiation. By doing so, it effectively prevents the development of drug resistance, which is a major challenge in cancer treatment. This breakthrough holds great promise for improving the efficacy of cancer therapies involving RVT and radiation.[132] RVT can potentially reverse multidrug resistance, and the therapeutic effect of anticancer chemotherapy drugs can be enhanced by using smaller concentrations.[133] In particular, multidrug resistance can be reversed by using small-molecule compound inhibitors to target P-glycoprotein encoded by the MDR1 gene. P-glycoprotein is a member of the ATP-binding cassette transporter family and a multidrug resistance protein, and is the most common cause of multidrug resistance in tumors.[134] RVT can inhibit the progression of glioblastoma cells and reverses chemoresistance by suppressing AKT and P-glycoprotein.[135]

The use of platinum drugs is limited by adverse effects, which can be severe. Drug resistance often occurs due to changes in different molecular aspects during treatment, resulting in treatment failure and tumor recurrence.[136–138] The combined use of RVT and platinum drugs can increase the chemosensitivity of cancer cells. Research by Nessa *et al*. has shown that when cisplatin and oxaliplatin are used in combination with RVT, A2780 OC cells become sensitive to cisplatin and oxaliplatin by down-regulating NF-κB,[139] and another study demonstrated a 3.1-fold increase in cisplatin cytotoxicity against A2780 cells after 48 hours of RVT pretreatment.[140]

The mechanisms of cell resistance are multifactorial and involve complex interactions between intracellular changes and the tumor microenvironment.[141] An emerging strategy to overcome resistance is the combination of inhibitors targeted to multiple pathways. In particular, inhibition of several signaling pathways at the same time produces better antitumor activity than inhibition of any one signaling pathway alone.[142,143] The multicenter, combined, randomized Phase 2 TRIAS trial compared the combination of the multiple kinase inhibitors sorafenib and topotecan as maintenance therapy for platinum-resistant or platinum-refractory OC, and the results showed that the multitarget strategy of sorafenib combined with topotecan produced a statistically and clinically significant improvement in progression-free survival for women with platinum-resistant OC.[144] In particular, the progression-free survival of the sorafenib group was significantly increased compared with placebo (risk ratio, 0.60; 95% CI, 0.43–0.83; p = 0.0018).The various effects and molecular targets of RVT nanoformulations involved in OC are detailed in Table 3.[93–95,97,98,113]

Clinical trial of RVT on ovarian metabolic diseases

We searched PubMed, ScienceDirect, Google Scholar, Scopus, ISI Web of Science, ProQuest, Embase databases, and ClinicalTrials (https:// ClinicalTrials.gov/) from 2001 to 2025 using relevant keywords. Although there are substantial data on the use of RVT in clinical trials, we did not find any clinical trials in which RVT was directly used in OC. Researchers are more concerned about ovarian metabolic diseases.

This clinical evidence indicates that RVT plays a beneficial role in ovarian metabolic diseases. Judging from the clinical outcomes, these effects have multiple positive implications. For patients with primary ovarian insufficiency, clinical studies have found that RVT may help improve the endocrine function of the ovaries. By regulating hormone levels in the body, it can alleviate the hormonal imbalance caused by the decline of ovarian function to a certain extent.[145] The role of RVT in preventing ovarian metabolic diseases should not be ignored either. Clinical studies have shown that RVT can regulate metabolic parameters in patients with polycystic ovary syndrome. Long-term use of RVT has alleviated the symptoms of polycystic ovaries, reduced the number of small follicles in the ovaries, and gradually restored normal hormone levels.[146–148]

A summary of human studies on the effects of RVT on ovarian metabolic diseases is presented in Table 4.[145–48]

The potential use of RVT for treating OC is not only based on targeting a specific gene or protein, but also on the regulation of various aspects of cancer cell growth through synergistic effects on multiple targets. This potency comes from the fact that RVT has a structure comprising two benzene rings, which have a conjugate effect and can form strong hydrophobic action bonds with target proteins, and the hydroxyl groups of polyphenols can form hydrogen bonds with amino acid residues in the structural domains of proteins.[19–21] Consequently, the cavity-specific combination of RVT and relevant proteins is harnessed to play a role in treating OC. A single chemical compound thus provides a multitarget and holistic disease treatment strategy. RVT can also play different roles at various stages in the occurrence and development of OC.[14]

Future perspective

In the treatment of OC, the use of multiple targets and pathways is suggested to provide a new strategy to overcome resistance that

Table 4. Summary of clinical trials on RVT in ovarian metabolic diseases

Source of evidence	Sample size	Dosage and type of administration	Study duration	Result
145	63	Unknown	6 months	Decrease: fasting glucose (p = 0.002), BMI (p = 0.005), and oxidative stress marker MDA (p < 0.001). Increase: BMI, ovarian volume, Ferriman-Gallwey Score (FGS), LH levels, and quality of life.
146	78	100mg/day	3 months	Decrease: hair loss (p = 0.009). Increase: menstruation rate (p = 0.03).
147	61	800mg/day	40 days	Decrease: expression of VEGF and HIF1 (p = 0.001). Increase: serun levels of FSH and TSH (p < 0.05).
148	34	1,500 mg/day	3 months	Decrease: fasting insulin level (p = 0.007). Increase: insulin sensitivity index (p = 0.04).

BMI, body mass Index; FSH, follicle-stimulating hormone; HIF1, hypoxia-inducible factor 1; LH, luteinizing hormone; MDA, malondialdehyde; RVT, resveratrol; TSH, thyroid-stimulating hormone; VEGF, vascular endothelial growth factor.

may develop to conventional drugs used for treating OC. Presently, although the beneficial effect of RVT in treating OC has been observed in a large number of *in vitro* studies and in some *in vivo* studies, there are still many challenges to address before RVT can be used in routine clinical practice. In particular, more clinical data are needed to prove the therapeutic potential of RVT, and more pharmacokinetic studies are required before the substance is marketed as a prescription drug. In addition, studies on the standardization of extracts and dosage forms are needed. By changing the dosage form and the method of drug encapsulation, such as adding metal ions to form novel drugs, including nanomaterials of complexes, liposomes, and the like, and using imaging techniques such as MRI to study effects and outcomes, it will be possible to establish whether and how RVT might be used to effectively treat OC.

Conclusions

RVT represents a compelling multitargeted therapeutic approach for OC, offering a distinct advantage over conventional single-target agents. Its unique molecular architecture facilitates specific interactions with key regulatory proteins, enabling the simultaneous modulation of multiple signaling pathways implicated in cancer cell proliferation and disease progression. This integrative mechanism of action holds significant potential to address drug resistance, a major obstacle in the clinical management of OC. Although robust preclinical evidence from both *in vitro* and *in vivo* models demonstrates RVT's efficacy and therapeutic promise, substantial translational challenges remain. The successful advancement of RVT into clinical practice will require comprehensive pharmacokinetic evaluation, standardized formulation development, and well-designed clinical trials to definitively establish its safety and therapeutic benefits. Future research should prioritize optimizing delivery strategies through innovative formulations and leverage advanced imaging technologies to validate target engagement and treatment response, thereby accelerating the translation of promising preclinical findings into tangible clinical outcomes for patients with OC.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Conceptualization, writing original draft (YC, DP), analysis and interpretation of data (BD, MZ, ZQ), critical revision of the manuscript for important intellectual content (NR, BQ), data curation (JW, FW, SJ), supervision, and project administration (YL). All authors have made significant contributions to this study and have approved the final manuscript.

References

[1] Nersesian S, Glazebrook H, Toulany J, Grantham SR, Boudreau JE. Naturally Killing the Silent Killer: NK Cell-Based Immunotherapy for Ovarian Cancer. Front Immunol 2019;10:1782. doi:10.3389/fimmu.2019.01782, PMID:31456796.

[2] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74(1):12–49. doi:10.3322/caac.21820, PMID:38230766.

[3] Mallen A, Soong TR, Townsend MK, Wenham RM, Crum CP, Tworoger SS. Surgical prevention strategies in ovarian cancer. Gynecol Oncol 2018;151(1):166–175. doi:10.1016/j.ygyno.2018.08.005, PMID:30087058.

[4] Stewart SL, Rim SH, Richards TB. Gynecologic oncologists and ovarian cancer treatment: avenues for improved survival. J Womens Health (Larchmt)2011;20(9):1257–1260.doi:10.1089/jwh.2011.3053,PMID:21819252.

[5] Lim A, Mesher D, Gentry-Maharaj A, Balogun N, Widschwendter M, Jacobs I, *et al*. Time to diagnosis of Type I or II invasive epithelial ovarian cancers: a multicentre observational study using patient questionnaire and primary care records. BJOG 2016;123(6):1012–1020. doi:10.1111/1471-0528.13447, PMID:26032603.

[6] Zattoni IF, Delabio LC, Dutra JP, Kita DH, Scheiffer G, Hembecker M, *et al*. Targeting breast cancer resistance protein (BCRP/ABCG2): Functional inhibitors and expression modulators. Eur J Med Chem 2022;237:114346. doi:10.1016/j.ejmech.2022.114346, PMID:35483322.

[7] Marchetti C, De Felice F, Romito A, Iacobelli V, Sassu CM, Corrado G, *et al*. Chemotherapy resistance in epithelial ovarian cancer: Mecha-

nisms and emerging treatments. Semin Cancer Biol 2021;77:144–166. doi:10.1016/j.semcancer.2021.08.011, PMID:34464704.
[8] Yousef M, Vlachogiannis IA, Tsiani E. Effects of Resveratrol against Lung Cancer: In Vitro and In Vivo Studies. Nutrients 2017;9(11):1231. doi:10.3390/nu9111231, PMID:29125563.
[9] Fenner A. Prostate cancer: Resveratrol inhibits the AR. Nat Rev Urol 2017;14(11):642. doi:10.1038/nrurol.2017.159, PMID:28976500.
[10] Xu XL, Deng SL, Lian ZX, Yu K. Resveratrol Targets a Variety of Oncogenic and Oncosuppressive Signaling for Ovarian Cancer Prevention and Treatment. Antioxidants (Basel) 2021;10(11):1718. doi:10.3390/antiox10111718, PMID:34829589.
[11] Angellotti G, Di Prima G, Belfiore E, Campisi G, De Caro V. Chemopreventive and Anticancer Role of Resveratrol against Oral Squamous Cell Carcinoma. Pharmaceutics 2023;15(1):275. doi:10.3390/pharmaceutics15010275, PMID:36678905.
[12] Campos-Toimil M, Elíes J, Alvarez E, Verde I, Orallo F. Effects of trans- and cis-resveratrol on Ca2+ handling in A7r5 vascular myocytes. Eur J Pharmacol 2007;577(1-3):91–99. doi:10.1016/j.ejphar.2007.08.003, PMID:17822692.
[13] Neyra Recky JR, Gaspar Tosato M, Buglak AA, Dántola ML, Lorente C. Photosensitized isomerization of resveratrol: Evaluation of energy and electron transfer pathways. Free Radic Biol Med 2024;216:50–59. doi:10.1016/j.freeradbiomed.2024.01.038, PMID:38272325.
[14] Ren B, Kwah MX, Liu C, Ma Z, Shanmugam MK, Ding L, *et al*. Resveratrol for cancer therapy: Challenges and future perspectives. Cancer Lett 2021;515:63–72. doi:10.1016/j.canlet.2021.05.001, PMID:34052324.
[15] Réthoré L, Guihot AL, Grimaud L, Proux C, Barré B, Guillonneau F, *et al*. A Novel Function of Na(V) Channel β3 Subunit in Endothelial Cell Alignment Through Autophagy Modulation. FASEB J 2025;39(11):e70663. doi:10.1096/fj.202401558RR, PMID:40445729.
[16] Lohse I, Wildermuth E, Brothers SP. Naturally occurring compounds as pancreatic cancer therapeutics. Oncotarget 2018;9(83):35448–35457. doi:10.18632/oncotarget.26234, PMID:30459936.
[17] Thipe VC, Raphael Karikachery A, Katti K, Katti KV. Immunomodulatory and tumor-targeting palladium nanoparticles functionalized with resveratrol via green nanotechnology: synthesis, mechanisms, and in vivo therapeutic evaluation. J Mater Chem B 2025;13(29):8683–8704. doi:10.1039/D5TB00620A.
[18] Wang F, Chatterjee S. Dominant Carbons in trans- and cis-Resveratrol Isomerization. J Phys Chem B 2017;121(18):4745–4755. doi:10.1021/acs.jpcb.7b02115, PMID:28402662.
[19] Liu M, Liu T, Shi Y, Zhao Y, Yan H, Sun B, *et al*. Comparative study on the interaction of oxyresveratrol and piceatannol with trypsin and lysozyme: binding ability, activity and stability. Food Funct 2019;10(12):8182–8194. doi:10.1039/c9fo01888c, PMID:31696185.
[20] Hu Q, Luo Y. Polyphenol-chitosan conjugates: Synthesis, characterization, and applications. Carbohydr Polym 2016;151:624–639. doi:10.1016/j.carbpol.2016.05.109, PMID:27474608.
[21] Vittorio O, Curcio M, Cojoc M, Goya GF, Hampel S, Iemma F, *et al*. Polyphenols delivery by polymeric materials: challenges in cancer treatment. Drug Deliv 2017;24(1):162–180. doi:10.1080/10717544.2016.1236846, PMID:28156178.
[22] Cirillo G, Curcio M, Vittorio O, Iemma F, Restuccia D, Spizzirri UG, *et al*. Polyphenol Conjugates and Human Health: A Perspective Review. Crit Rev Food Sci Nutr 2016;56(2):326–337. doi:10.1080/10408398.2012.752342, PMID:24867371.
[23] Paggi JM, Pandit A, Dror RO. The Art and Science of Molecular Docking. Annu Rev Biochem 2024;93(1):389–410. doi:10.1146/annurev-biochem-030222-120000, PMID:38594926.
[24] Yang X, Potts PR. CSAG2 is a cancer-specific activator of SIRT1. EMBO Rep 2020;21(9):e50912. doi:10.15252/embr.202050912, PMID:32761762.
[25] Wang S, Zhang J, Ma L, inventors; Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, assignee. The application of SIRT1 in the preparation of drugs for protecting ovarian function. China patent CN112933215A. 2021 Jun 11.
[26] Roy S, Das A, Vernekar M, Das S, Chatterjee N. Abstract 2461: SIRT1 regulates ovarian cancer metastasis via altering the exosome release and glycogen deposition. Cancer Res 2021;81(13_Suppl):2461. doi:10.1158/1538-7445.AM2021-2461.
[27] Rayalam S, Della-Fera MA, Baile CA. Synergism between resveratrol and other phytochemicals: implications for obesity and osteoporosis. Mol Nutr Food Res 2011;55(8):1177–1185. doi:10.1002/mnfr.201000616, PMID:21538845.
[28] Jang KY, Kim KS, Hwang SH, Kwon KS, Kim KR, Park HS, *et al*. Expression and prognostic significance of SIRT1 in ovarian epithelial tumours. Pathology 2009;41(4):366–371. doi:10.1080/00313020902884451, PMID:19404850.
[29] Sevgin K, Erguven P. SIRT1 overexpression by melatonin and resveratrol combined treatment attenuates premature ovarian failure through activation of SIRT1/FOXO3a/BCL2 pathway. Biochem Biophys Res Commun 2024;696:149506. doi:10.1016/j.bbrc.2024.149506, PMID:38224665.
[30] Kwon KJ, Kim HJ, Shin CY, Han SH. Melatonin Potentiates the Neuroprotective Properties of Resveratrol Against Beta-Amyloid-Induced Neurodegeneration by Modulating AMP-Activated Protein Kinase Pathways. J Clin Neurol 2010;6(3):127–137. doi:10.3988/jcn.2010.6.3.127, PMID:20944813.
[31] Bagul PK, Dinda AK, Banerjee SK. Effect of resveratrol on sirtuins expression and cardiac complications in diabetes. Biochem Biophys Res Commun 2015;468(1-2):221–227. doi:10.1016/j.bbrc.2015.10.126, PMID:26518647.
[32] Wang R, Yuan W, Li L, Lu F, Zhang L, Gong H, *et al*. Resveratrol ameliorates muscle atrophy in chronic kidney disease via the axis of SIRT1/FoxO1. Phytother Res 2022;36(8):3265–3275. doi:10.1002/ptr.7499, PMID:35606908.
[33] Saqib U, Kelley TT, Panguluri SK, Liu D, Savai R, Baig MS, *et al*. Polypharmacology or Promiscuity? Structural Interactions of Resveratrol With Its Bandwagon of Targets. Front Pharmacol 2018;9:1201. doi:10.3389/fphar.2018.01201, PMID:30405416.
[34] Scott KF, Sajinovic M, Hein J, Nixdorf S, Galettis P, Liauw W, *et al*. Emerging roles for phospholipase A2 enzymes in cancer. Biochimie 2010;92(6):601–610. doi:10.1016/j.biochi.2010.03.019, PMID:20362028.
[35] Amalinei C, Păvăleanu I, Balan RA. Involvement of phospholipase A_2 in gynecological cancer. In: Chakraborti S (ed). Phospholipases in Physiology and Pathology. Vol 3. Amsterdam: Academic Press; 2023:15–37. doi:10.1016/B978-0-323-95697-0.00017-0.
[36] Gao Y, Yang Z, Bajpai AK, Wang W, Zhang L, Xia Z. Resveratrol enhances the antiliver cancer effect of cisplatin by targeting the cell membrane protein PLA2. Front Oncol 2024;14:1453164. doi:10.3389/fonc.2024.1453164, PMID:39381045.
[37] Eder AM, Sasagawa T, Mao M, Aoki J, Mills GB. Constitutive and lysophosphatidic acid (LPA)-induced LPA production: role of phospholipase D and phospholipase A2. Clin Cancer Res 2000;6(6):2482–2491. PMID:10873103.
[38] Ray U, Roy D, Jin L, Thirusangu P, Staub J, Xiao Y, *et al*. Group III phospholipase A2 downregulation attenuated survival and metastasis in ovarian cancer and promotes chemo-sensitization. J Exp Clin Cancer Res 2021;40(1):182. doi:10.1186/s13046-021-01985-9, PMID:34082797.
[39] Sharifpour S, Fakhraee S, Behjatmanesh-Ardakani R. Insights into the mechanism of inhibition of phospholipase A2 by resveratrol: An extensive molecular dynamics simulation and binding free energy calculation. J Mol Graph Model 2020;100:107649. doi:10.1016/j.jmgm.2020.107649, PMID:32739638.
[40] Shukla PK, Gautam L, Sinha M, Kaur P, Sharma S, Singh TP. Structures and binding studies of the complexes of phospholipase A2 with five inhibitors. Biochim Biophys Acta 2015;1854(4):269–277. doi:10.1016/j.bbapap.2014.12.017, PMID:25541253.
[41] Chan KKL, Siu MKY, Jiang YX, Wang JJ, Wang Y, Leung THY, *et al*. Differential expression of estrogen receptor subtypes and variants in ovarian cancer: effects on cell invasion, proliferation and prognosis. BMC Cancer 2017;17(1):606. doi:10.1186/s12885-017-3601-1, PMID:28859612.
[42] Sieh W, Köbel M, Longacre TA, Bowtell DD, deFazio A, Goodman MT, *et al*. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. Lancet Oncol 2013;14(9):853–862. doi:10.1016/S1470-2045(13)70253-5, PMID:23845225.
[43] Li S, Jiang K, Li J, Hao X, Chu W, Luo C, *et al*. Estrogen enhances the proliferation and migration of ovarian cancer cells by activating transient receptor potential channel C3. J Ovarian Res 2020;13(1):20.

doi:10.1186/s13048-020-00621-y, PMID:32087757.
[44] Kozieł MJ, Piastowska-Ciesielska AW. Estrogens, Estrogen Receptors and Tumor Microenvironment in Ovarian Cancer. Int J Mol Sci 2023;24(19):14673. doi:10.3390/ijms241914673, PMID:37834120.
[45] Qasem RJ. The estrogenic activity of resveratrol: a comprehensive review of in vitro and in vivo evidence and the potential for endocrine disruption. Crit Rev Toxicol 2020;50(5):439–462. doi:10.1080/10408444.2020.1762538, PMID:32744480.
[46] Chakraborty S, Levenson AS, Biswas PK. Structural insights into Resveratrol's antagonist and partial agonist actions on estrogen receptor alpha. BMC Struct Biol 2013;13:27. doi:10.1186/1472-6807-13-27, PMID:24160181.
[47] Vignati S, Albertini V, Rinaldi A, Kwee I, Riva C, Oldrini R, *et al*. Cellular and molecular consequences of peroxisome proliferator-activated receptor-gamma activation in ovarian cancer cells. Neoplasia 2006;8(10):851–861. doi:10.1593/neo.06433, PMID:17032502.
[48] Plutzky J. The PPAR-RXR transcriptional complex in the vasculature: energy in the balance. Circ Res 2011;108(8):1002–1016. doi:10.1161/CIRCRESAHA.110.226860, PMID:21493923.
[49] Prat M, Coulson K, Blot C, Jacquemin G, Romano M, Renoud ML, *et al*. PPARγ activation modulates the balance of peritoneal macrophage populations to suppress ovarian tumor growth and tumor-induced immunosuppression. J Immunother Cancer 2023;11(8):e007031. doi:10.1136/jitc-2023-007031, PMID:37586764.
[50] Alhakamy NA, Alamoudi AJ, Abdulaal WH, Choudhry H, Asfour HZ, Al-Rabia MW, *et al*. Celastrol protects against cisplatin-induced ovarian toxicity via modulation of PPAR-γ and AMPK. Naunyn Schmiedebergs Arch Pharmacol 2025;398(12):17267–17276. doi:10.1007/s00210-025-04322-5, PMID:40481255.
[51] Yu YH, Chang YC, Su TH, Nong JY, Li CC, Chuang LM. Prostaglandin reductase-3 negatively modulates adipogenesis through regulation of PPARγ activity. J Lipid Res 2013;54(9):2391–2399. doi:10.1194/jlr.M037556, PMID:23821743.
[52] Calleri E, Pochetti G, Dossou KSS, Laghezza A, Montanari R, Capelli D, *et al*. Resveratrol and its metabolites bind to PPARs. Chembiochem 2014;15(8):1154–1160. doi:10.1002/cbic.201300754, PMID:24796862.
[53] Zinger A, Cho WC, Ben-Yehuda A. Cancer and Aging - the Inflammatory Connection. Aging Dis 2017;8(5):611–627. doi:10.14336/AD.2016.1230, PMID:28966805.
[54] Tang F, Wang Y, Hemmings BA, Rüegg C, Xue G. PKB/Akt-dependent regulation of inflammation in cancer. Semin Cancer Biol 2018;48:62–69. doi:10.1016/j.semcancer.2017.04.018, PMID:28476657.
[55] Yang L, Lin PC. Mechanisms that drive inflammatory tumor microenvironment, tumor heterogeneity, and metastatic progression. Semin Cancer Biol 2017;47:185–195. doi:10.1016/j.semcancer.2017.08.001, PMID:28782608.
[56] Rietschel ET, Kirikae T, Schade FU, Mamat U, Schmidt G, Loppnow H, *et al*. Bacterial endotoxin: molecular relationships of structure to activity and function. FASEB J 1994;8(2):217–225. doi:10.1096/fasebj.8.2.8119492, PMID:8119492.
[57] Kim KT, Heo JB, Roh T, Jeon SM, Heo HJ, Choi YJ, *et al*. Resveratrol derivative SH-707 inhibits NLRP3 inflammasome activation via a sirtuin 1-dependent pathway. Int Immunopharmacol 2025;161:115049. doi:10.1016/j.intimp.2025.115049, PMID:40523327.
[58] Zhong LM, Zong Y, Sun L, Guo JZ, Zhang W, He Y, *et al*. Resveratrol inhibits inflammatory responses via the mammalian target of rapamycin signaling pathway in cultured LPS-stimulated microglial cells. PLoS One 2012;7(2):e32195. doi:10.1371/journal.pone.0032195, PMID:22363816.
[59] Pinheiro DML, de Oliveira AHS, Coutinho LG, Fontes FL, de Medeiros Oliveira RK, Oliveira TT, *et al*. Resveratrol decreases the expression of genes involved in inflammation through transcriptional regulation. Free Radic Biol Med 2019;130:8–22. doi:10.1016/j.freeradbiomed.2018.10.432, PMID:30366059.
[60] Panaro MA, Carofiglio V, Acquafredda A, Cavallo P, Cianciulli A. Anti-inflammatory effects of resveratrol occur via inhibition of lipopolysaccharide-induced NF-κB activation in Caco-2 and SW480 human colon cancer cells. Br J Nutr 2012;108(9):1623–1632. doi:10.1017/S0007114511007227, PMID:22251620.
[61] Ma C, Wang Y, Dong L, Li M, Cai W. Anti-inflammatory effect of resveratrol through the suppression of NF-κB and JAK/STAT signaling pathways. Acta Biochim Biophys Sin (Shanghai) 2015;47(3):207–213. doi:10.1093/abbs/gmu135, PMID:25651848.
[62] Dalal V, Kumar R, Kumar S, Sharma A, Kumar L, Sharma JB, *et al*. Biomarker potential of IL-6 and VEGF-A in ascitic fluid of epithelial ovarian cancer patients. Clin Chim Acta 2018;482:27–32. doi:10.1016/j.cca.2018.03.019, PMID:29572186.
[63] Ferraresi A, Phadngam S, Morani F, Galetto A, Alabiso O, Chiorino G, *et al*. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. Mol Carcinog 2017;56(3):1164–1181. doi:10.1002/mc.22582, PMID:27787915.
[64] Wang T, Wu F, Jin Z, Zhai Z, Wang Y, Tu B, *et al*. Plumbagin inhibits LPS-induced inflammation through the inactivation of the nuclear factor-kappa B and mitogen activated protein kinase signaling pathways in RAW 264.7 cells. Food Chem Toxicol 2014;64:177–183. doi:10.1016/j.fct.2013.11.027, PMID:24296134.
[65] Tsai SH, Lin-Shiau SY, Lin JK. Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol. Br J Pharmacol 1999;126(3):673–680. doi:10.1038/sj.bjp.0702357, PMID:10188978.
[66] Saiko P, Szakmary A, Jaeger W, Szekeres T. Resveratrol and its analogs: defense against cancer, coronary disease and neurodegenerative maladies or just a fad? Mutat Res 2008;658(1-2):68–94. doi:10.1016/j.mrrev.2007.08.004, PMID:17890139.
[67] Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, *et al*. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J 2004;23(12):2369–2380. doi:10.1038/sj.emboj.7600244, PMID:15152190.
[68] Bonizzi G, Karin M. The two NF-kappaB activation pathways and their role in innate and adaptive immunity. Trends Immunol 2004;25(6):280–288. doi:10.1016/j.it.2004.03.008, PMID:15145317.
[69] Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative Stress in Cancer. Cancer Cell 2020;38(2):167–197. doi:10.1016/j.ccell.2020.06.001, PMID:32649885.
[70] Lin BW, Gong CC, Song HF, Cui YY. Effects of anthocyanins on the prevention and treatment of cancer. Br J Pharmacol 2017;174(11):1226–1243. doi:10.1111/bph.13627, PMID:27646173.
[71] Jiang Y, Song L, Lin Y, Nowialis P, Gao Q, Li T, *et al*. ROS-mediated SRMS activation confers platinum resistance in ovarian cancer. Oncogene 2023;42(20):1672–1684. doi:10.1038/s41388-023-02679-6, PMID:37020040.
[72] Burns J, Yokota T, Ashihara H, Lean ME, Crozier A. Plant foods and herbal sources of resveratrol. J Agric Food Chem 2002;50(11):3337–3340. doi:10.1021/jf0112973, PMID:12010007.
[73] Seino M, Okada M, Shibuya K, Seino S, Suzuki S, Takeda H, *et al*. Differential contribution of ROS to resveratrol-induced cell death and loss of self-renewal capacity of ovarian cancer stem cells. Anticancer Res 2015;35(1):85–96. PMID:25550538.
[74] Ibrahim MA, Albahlol IA, Wani FA, Abd-Eltawab Tammam A, Kelleni MT, Sayeed MU, *et al*. Resveratrol protects against cisplatin-induced ovarian and uterine toxicity in female rats by attenuating oxidative stress, inflammation and apoptosis. Chem Biol Interact 2021;338:109402. doi:10.1016/j.cbi.2021.109402, PMID:33587916.
[75] Hu X, Yuan Z, Huang G, Chen M, Chen T, He L. High-Valence selenium nanotherapeutics downregulates MUC16 to drive precise ovarian cancer therapy through redox perturbation. Adv Funct Mater 2025;35(22):2419242. doi:10.1002/adfm.202419242.
[76] Gu T, Wang N, Wu T, Ge Q, Chen L. Antioxidative stress mechanisms behind resveratrol: a multidimensional analysis. J Food Qual 2021;2021(1):5571733. doi:10.1155/2021/5571733.
[77] Whittaker SR, Mallinger A, Workman P, Clarke PA. Inhibitors of cyclin-dependent kinases as cancer therapeutics. Pharmacol Ther 2017;173:83–105. doi:10.1016/j.pharmthera.2017.02.008, PMID:28174091.
[78] Huang KC, Yang J, Ng MC, Ng SK, Welch WR, Muto MG, *et al*. Cyclin A1 expression and paclitaxel resistance in human ovarian cancer cells. Eur J Cancer 2016;67:152–163. doi:10.1016/j.ejca.2016.08.007, PMID:27669502.
[79] Vergara D, Simeone P, Toraldo D, Del Boccio P, Vergaro V, Leporatti S, *et al*. Resveratrol downregulates Akt/GSK and ERK signalling pathways in OVCAR-3 ovarian cancer cells. Mol Biosyst 2012;8(4):1078–1087.

doi:10.1039/c2mb05486h, PMID:22234583.
[80] Thaklaewphan P, Wikan N, Potikanond S, Nimlamool W. Oxyresveratrol Enhances the Anti-Cancer Effect of Cisplatin against Epithelial Ovarian Cancer Cells through Suppressing the Activation of Protein Kinase B (AKT). Biomolecules 2024;14(9):1140. doi:10.3390/biom14091140, PMID:39334906.
[81] Hankittichai P, Thaklaewphan P, Wikan N, Ruttanapattanakul J, Potikanond S, Smith DR, *et al*. Resveratrol Enhances Cytotoxic Effects of Cisplatin by Inducing Cell Cycle Arrest and Apoptosis in Ovarian Adenocarcinoma SKOV-3 Cells through Activating the p38 MAPK and Suppressing AKT. Pharmaceuticals (Basel) 2023;16(5):755. doi:10.3390/ph16050755, PMID:37242538.
[82] Zhong LX, Li H, Wu ML, Liu XY, Zhong MJ, Chen XY, *et al*. Inhibition of STAT3 signaling as critical molecular event in resveratrol-suppressed ovarian cancer cells. J Ovarian Res 2015;8:25. doi:10.1186/s13048-015-0152-4, PMID:25896424.
[83] Wahba J, Natoli M, Whilding LM, Parente-Pereira AC, Jung Y, Zona S, *et al*. Chemotherapy-induced apoptosis, autophagy and cell cycle arrest are key drivers of synergy in chemo-immunotherapy of epithelial ovarian cancer. Cancer Immunol Immunother 2018;67(11):1753–1765. doi:10.1007/s00262-018-2199-8, PMID:30167862.
[84] Stivala LA, Savio M, Carafoli F, Perucca P, Bianchi L, Maga G, *et al*. Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. J Biol Chem 2001;276(25):22586–22594. doi:10.1074/jbc.M101846200, PMID:11316812.
[85] Liu Y, Tong L, Luo Y, Li X, Chen G, Wang Y. Resveratrol inhibits the proliferation and induces the apoptosis in ovarian cancer cells via inhibiting glycolysis and targeting AMPK/mTOR signaling pathway. J Cell Biochem 2018;119(7):6162–6172. doi:10.1002/jcb.26822, PMID:29663499.
[86] de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. Mol Nutr Food Res 2005;49(5):405–430. doi:10.1002/mnfr.200500022, PMID:15832402.
[87] Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell 1998;93(5):705–716. doi:10.1016/s0092-8674(00)81433-6, PMID:9630216.
[88] Lin C, Crawford DR, Lin S, Hwang J, Sebuyira A, Meng R, *et al*. Inducible COX-2-dependent apoptosis in human ovarian cancer cells. Carcinogenesis 2011;32(1):19–26. doi:10.1093/carcin/bgq212, PMID:21187340.
[89] Lin HY, Tang HY, Davis FB, Davis PJ. Resveratrol and apoptosis. Ann N Y Acad Sci 2011;1215:79–88. doi:10.1111/j.1749-6632.2010.05846.x, PMID:21261644.
[90] Jin S, Wei J, You L, Liu H, Qian W. Autophagy regulation and its dual role in blood cancers: A novel target for therapeutic development (Review). Oncol Rep 2018;39(6):2473–2481. doi:10.3892/or.2018.6370, PMID:29658589.
[91] Barnard RA, Regan DP, Hansen RJ, Maycotte P, Thorburn A, Gustafson DL. Autophagy Inhibition Delays Early but Not Late-Stage Metastatic Disease. J Pharmacol Exp Ther 2016;358(2):282–293. doi:10.1124/jpet.116.233908, PMID:27231155.
[92] Guo JY, Xia B, White E. Autophagy-mediated tumor promotion. Cell 2013;155(6):1216–1219. doi:10.1016/j.cell.2013.11.019, PMID:24315093.
[93] Long W, Zhang L, Wang Y, Xie H, Wang L, Yu H. Research Progress and Prospects of Autophagy in the Mechanism of Multidrug Resistance in Tumors. J Oncol 2022;2022:7032614. doi:10.1155/2022/7032614, PMID:35136409.
[94] White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer 2012;12(6):401–410. doi:10.1038/nrc3262, PMID:22534666.
[95] Ferraresi A, Girone C, Esposito A, Vidoni C, Vallino L, Secomandi E, *et al*. How Autophagy Shapes the Tumor Microenvironment in Ovarian Cancer. Front Oncol 2020;10:599915. doi:10.3389/fonc.2020.599915, PMID:33364196.
[96] Wang Q, Bu S, Xin D, Li B, Wang L, Lai D. Autophagy Is Indispensable for the Self-Renewal and Quiescence of Ovarian Cancer Spheroid Cells with Stem Cell-Like Properties. Oxid Med Cell Longev 2018;2018:7010472. doi:10.1155/2018/7010472, PMID:30319732.
[97] Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. Mol Cancer 2020;19(1):12. doi:10.1186/s12943-020-1138-4, PMID:31969156.
[98] Zhong LX, Zhang Y, Wu ML, Liu YN, Zhang P, Chen XY, *et al*. Resveratrol and STAT inhibitor enhance autophagy in ovarian cancer cells. Cell Death Discov 2016;2:15071. doi:10.1038/cddiscovery.2015.71, PMID:27551495.
[99] Ferraresi A, Esposito A, Girone C, Vallino L, Salwa A, Ghezzi I, *et al*. Resveratrol Contrasts LPA-Induced Ovarian Cancer Cell Migration and Platinum Resistance by Rescuing Hedgehog-Mediated Autophagy. Cells 2021;10(11):3213. doi:10.3390/cells10113213, PMID:34831435.
[100] Hu S, Li X, Xu R, Ye L, Kong H, Zeng X, *et al*. The synergistic effect of resveratrol in combination with cisplatin on apoptosis via modulating autophagy in A549 cells. Acta Biochim Biophys Sin (Shanghai) 2016;48(6):528–535. doi:10.1093/abbs/gmw026, PMID:27084520.
[101] Vidoni C, Ferraresi A, Vallino L, Salwa A, Ha JH, Seca C, *et al*. Glycolysis Inhibition of Autophagy Drives Malignancy in Ovarian Cancer: Exacerbation by IL-6 and Attenuation by Resveratrol. Int J Mol Sci 2023;24(2):1723. doi:10.3390/ijms24021723, PMID:36675246.
[102] Opipari AW Jr, Tan L, Boitano AE, Sorenson DR, Aurora A, Liu JR. Resveratrol-induced autophagocytosis in ovarian cancer cells. Cancer Res 2004;64(2):696–703. doi:10.1158/0008-5472.can-03-2404, PMID:14744787.
[103] Rauf A, Imran M, Butt MS, Nadeem M, Peters DG, Mubarak MS. Resveratrol as an anti-cancer agent: A review. Crit Rev Food Sci Nutr 2018;58(9):1428–1447. doi:10.1080/10408398.2016.1263597, PMID:28001084.
[104] Singh AP, Singh R, Verma SS, Rai V, Kaschula CH, Maiti P, *et al*. Health benefits of resveratrol: Evidence from clinical studies. Med Res Rev 2019;39(5):1851–1891. doi:10.1002/med.21565, PMID:30741437.
[105] Elias KM, Guo J, Bast RC Jr. Early Detection of Ovarian Cancer. Hematol Oncol Clin North Am 2018;32(6):903–914. doi:10.1016/j.hoc.2018.07.003, PMID:30390764.
[106] Liu Y, Bhattarai P, Dai Z, Chen X. Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer. Chem Soc Rev 2019;48(7):2053–2108. doi:10.1039/c8cs00618k, PMID:30259015.
[107] Wang Y, Zhang H, Liu Y, Younis MH, Cai W, Bu W. Catalytic radiosensitization: Insights from materials physicochemistry. Mater Today (Kidlington) 2022;57:262–278. doi:10.1016/j.mattod.2022.05.022, PMID:36425004.
[108] Wang Z, Zhao Y, Yang Z, Li X, Xing H, Qu W, *et al*. Construction of Intelligent Responsive Drug Delivery System and Multi-Mode Imaging Based on Gold Nanodots. Macromol Rapid Commun 2022;43(10):e2200034. doi:10.1002/marc.202200034, PMID:35332623.
[109] Singh A, Guo Y, Cruz M, Shi D, Kitts DD, Pratap-Singh A. Chitosan/PEG nanoparticle-embedded oleogels improve blueberry derived resveratrol bioavailability and antioxidant capacity. Food Chem 2025;490:145038. doi:10.1016/j.foodchem.2025.145038, PMID:40505306.
[110] Sun Z, Cheng K, Yao Y, Wu F, Fung J, Chen H, *et al*. Controlled Nano-Bio Interface of Functional Nanoprobes for in Vivo Monitoring Enzyme Activity in Tumors. ACS Nano 2019;13(2):1153–1167. doi:10.1021/acsnano.8b05825, PMID:30673268.
[111] Khatun M, Choudhury S, Liu B, Lemmens P, Pal SK, Mazumder S. Resveratrol–ZnO nanohybrid enhanced anti-cancerous effect in ovarian cancer cells through ROS. RSC Adv 2016;6(107):105607–105617. doi:10.1039/C6RA16664D.
[112] Guo L, Peng Y, Li Y, Yao J, Zhang G, Chen J, *et al*. Cell death pathway induced by resveratrol-bovine serum albumin nanoparticles in a human ovarian cell line. Oncol Lett 2015;9(3):1359–1363. doi:10.3892/ol.2015.2851, PMID:25663913.
[113] Long Q, Zhu W, Guo L, Pu L. RGD-Conjugated Resveratrol HSA Nanoparticles as a Novel Delivery System in Ovarian Cancer Therapy. Drug Des Devel Ther 2020;14:5747–5756. doi:10.2147/DDDT.S248950, PMID:33408463.
[114] Chen Q, Gu P, Liu X, Hu S, Zheng H, Liu T, *et al*. Gold Nanoparticles Encapsulated Resveratrol as an Anti-Aging Agent to Delay Cataract Development. Pharmaceuticals (Basel) 2022;16(1):26. doi:10.3390/ph16010026, PMID:36678523.
[115] Wang M, Li L, Zhang X, Liu Y, Zhu R, Liu L, Fang Y, Gao Z, Gao D. Mag-

netic resveratrol liposomes as a new theranostic platform for magnetic resonance imaging guided Parkinson's disease targeting therapy. ACS Sustain Chem Eng 2018;6(12):17124–17133. doi:10.1021/acssuschemeng.8b04507.
[116] Carlson LJ, Cote B, Alani AW, Rao DA. Polymeric micellar co-delivery of resveratrol and curcumin to mitigate in vitro doxorubicin-induced cardiotoxicity. J Pharm Sci 2014;103(8):2315–2322. doi:10.1002/jps.24042, PMID:24914015.
[117] Fatease AA, Shah V, Nguyen DX, Cote B, LeBlanc N, Rao DA, *et al*. Chemosensitization and mitigation of Adriamycin-induced cardiotoxicity using combinational polymeric micelles for co-delivery of quercetin/resveratrol and resveratrol/curcumin in ovarian cancer. Nanomedicine 2019;19:39–48. doi:10.1016/j.nano.2019.03.011, PMID:31022465.
[118] Weżgowiec J, Łapińska Z, Lamch Ł, Szewczyk A, Saczko J, Kulbacka J, *et al*. Cytotoxic Activity of Curcumin- and Resveratrol-Loaded Core-Shell Systems in Resistant and Sensitive Human Ovarian Cancer Cells. Int J Mol Sci 2024;26(1):41. doi:10.3390/ijms26010041, PMID:39795900.
[119] van Jaarsveld MT, van Kuijk PF, Boersma AW, Helleman J, van IJcken WF, Mathijssen RH, *et al*. miR-634 restores drug sensitivity in resistant ovarian cancer cells by targeting the Ras-MAPK pathway. Mol Cancer 2015;14:196. doi:10.1186/s12943-015-0464-4, PMID:26576679.
[120] Cummings M, Freer C, Orsi NM. Targeting the tumour microenvironment in platinum-resistant ovarian cancer. Semin Cancer Biol 2021;77:3–28. doi:10.1016/j.semcancer.2021.02.007, PMID:33607246.
[121] Lupia M, Cavallaro U. Ovarian cancer stem cells: still an elusive entity? Mol Cancer 2017;16(1):64. doi:10.1186/s12943-017-0638-3, PMID:28320418.
[122] Cragg GM, Pezzuto JM. Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents. Med Princ Pract 2016;25(Suppl 2):41–59. doi:10.1159/000443404, PMID:26679767.
[123] Catanzaro D, Gabbia D, Cocetta V, Biagi M, Ragazzi E, Montopoli M, *et al*. Silybin counteracts doxorubicin resistance by inhibiting GLUT1 expression. Fitoterapia 2018;124:42–48. doi:10.1016/j.fitote.2017.10.007, PMID:29031537.
[124] Montopoli M, Ragazzi E, Froldi G, Caparrotta L. Cell-cycle inhibition and apoptosis induced by curcumin and cisplatin or oxaliplatin in human ovarian carcinoma cells. Cell Prolif 2009;42(2):195–206. doi:10.1111/j.1365-2184.2009.00585.x, PMID:19236381.
[125] Baatout S, Derradji H, Jacquet P, Ooms D, Michaux A, Mergeay M. Enhanced radiation-induced apoptosis of cancer cell lines after treatment with resveratrol. Int J Mol Med 2004;13(6):895–902. PMID:15138632.
[126] Xu L, Yang X, Cai J, Ma J, Cheng H, Zhao K, *et al*. Resveratrol attenuates radiation-induced salivary gland dysfunction in mice. Laryngoscope 2013;123(11):E23–E29. doi:10.1002/lary.24276, PMID:23794219.
[127] Carsten RE, Bachand AM, Bailey SM, Ullrich RL. Resveratrol reduces radiation-induced chromosome aberration frequencies in mouse bone marrow cells. Radiat Res 2008;169(6):633–638. doi:10.1667/RR1190.1, PMID:18494544.
[128] Wang L, Long L, Wang W, Liang Z. Resveratrol, a potential radiation sensitizer for glioma stem cells both in vitro and in vivo. J Pharmacol Sci 2015;129(4):216–225. doi:10.1016/j.jphs.2015.11.001, PMID:26698406.
[129] Mikami S, Ota I, Masui T, Uchiyama T, Okamoto H, Kimura T, *et al*. Resveratrol-induced REG III expression enhances chemo- and radiosensitivity in head and neck cancer in xenograft mice. Oncol Rep 2019;42(1):436–442. doi:10.3892/or.2019.7137, PMID:31059079.
[130] Chen YA, Lien HM, Kao MC, Lo UG, Lin LC, Lin CJ, *et al*. Sensitization of Radioresistant Prostate Cancer Cells by Resveratrol Isolated from Arachis hypogaea Stems. PLoS One 2017;12(1):e0169204. doi:10.1371/journal.pone.0169204, PMID:28081154.
[131] Zhang L, Ye B, Chen Z, Chen ZS. Progress in the studies on the molecular mechanisms associated with multidrug resistance in cancers. Acta Pharm Sin B 2023;13(3):982–997. doi:10.1016/j.apsb.2022.10.002, PMID:36970215.
[132] Zhu X, Zhang W, Xiang H, Chang Q, Liu R, Wan Y, *et al*. Radiation-enhanced self-cascade catalytic $Ti_3C_2T_x$-based platform enables controlled release of trans-resveratrol for synergistic radiosensitization against metastasis of orthotopic breast cancer. Nano Today 2023;50:101836. doi:10.1016/j.nantod.2023.101836.
[133] El-Readi MZ, Eid S, Abdelghany AA, Al-Amoudi HS, Efferth T, Wink M. Resveratrol mediated cancer cell apoptosis, and modulation of multidrug resistance proteins and metabolic enzymes. Phytomedicine 2019;55:269–281. doi:10.1016/j.phymed.2018.06.046, PMID:30668439.
[134] Zhang B, Kang Z, Zhang J, Kang Y, Liang L, Liu Y, *et al*. Simultaneous binding mechanism of multiple substrates for multidrug resistance transporter P-glycoprotein. Phys Chem Chem Phys 2021;23(8):4530–4543. doi:10.1039/d0cp05910b, PMID:33595579.
[135] Zhang Y, Zhang Z, Mousavi M, Moliani A, Bahman Y, Bagheri H. Resveratrol inhibits glioblastoma cells and chemoresistance progression through blockade P-glycoprotein and targeting AKT/PTEN signaling pathway. Chem Biol Interact 2023;376:110409. doi:10.1016/j.cbi.2023.110409.
[136] Galluzzi L, Vitale I, Michels J, Brenner C, Szabadkai G, Harel-Bellan A, *et al*. Systems biology of cisplatin resistance: past, present and future. Cell Death Dis 2014;5(5):e1257. doi:10.1038/cddis.2013.428, PMID:24874729.
[137] Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, *et al*. Molecular mechanisms of cisplatin resistance. Oncogene 2012;31(15):1869–1883. doi:10.1038/onc.2011.384, PMID:21892204.
[138] Cocetta V, Ragazzi E, Montopoli M. Links between cancer metabolism and cisplatin resistance. Int Rev Cell Mol Biol 2020;354:107–164. doi:10.1016/bs.ircmb.2020.01.005, PMID:32475471.
[139] Nessa MU, Beale P, Chan C, Yu JQ, Huq F. Combinations of resveratrol, cisplatin and oxaliplatin applied to human ovarian cancer cells. Anticancer Res 2012;32(1):53–59. PMID:22213288.
[140] Engelke LH, Hamacher A, Proksch P, Kassack MU. Ellagic Acid and Resveratrol Prevent the Development of Cisplatin Resistance in the Epithelial Ovarian Cancer Cell Line A2780. J Cancer 2016;7(4):353–363. doi:10.7150/jca.13754, PMID:26918049.
[141] McMullen M, Madariaga A, Lheureux S. New approaches for targeting platinum-resistant ovarian cancer. Semin Cancer Biol 2021;77:167–181. doi:10.1016/j.semcancer.2020.08.013, PMID:32871277.
[142] Khan IU, Khan RU, Asif H, Alamgeer, Khalid SH, Asghar S, *et al*. Co-delivery strategies to overcome multidrug resistance in ovarian cancer. Int J Pharm 2017;533(1):111–124. doi:10.1016/j.ijpharm.2017.09.060, PMID:28947245.
[143] Sohn EJ. PIK3R3, a regulatory subunit of PI3K, modulates ovarian cancer stem cells and ovarian cancer development and progression by integrative analysis. BMC Cancer 2022;22(1):708. doi:10.1186/s12885-022-09807-7, PMID:35761259.
[144] Chekerov R, Hilpert F, Mahner S, El-Balat A, Harter P, De Gregorio N, *et al*. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19(9):1247–1258. doi:10.1016/S1470-2045(18)30372-3, PMID:30100379.
[145] Zahra M, Shah M, Ahmad F, Zulfiqar F, Tariq A, Iqbal N. A randomized controlled trial comparing the efficacy of resveratrol combined with metformin versus resveratrol monotherapy in the management of polycystic ovary syndrome. Naunyn Schmiedebergs Arch Pharmacol 2025. doi:10.1007/s00210-025-04495-z, PMID:40888876.
[146] Mansour A, Samadi M, Sanginabadi M, Gerami H, Karimi S, Hosseini S, *et al*. Effect of resveratrol on menstrual cyclicity, hyperandrogenism and metabolic profile in women with PCOS. Clin Nutr 2021;40(6):4106–4112. doi:10.1016/j.clnu.2021.02.004, PMID:33610422.
[147] Bahramrezaie M, Amidi F, Aleyasin A, Saremi A, Aghahoseini M, Brenjian S, *et al*. Effects of resveratrol on VEGF & HIF1 genes expression in granulosa cells in the angiogenesis pathway and laboratory parameters of polycystic ovary syndrome: a triple-blind randomized clinical trial. J Assist Reprod Genet 2019;36(8):1701–1712. doi:10.1007/s10815-019-01461-6, PMID:31327131.
[148] Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L, Duleba AJ. Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial. J Clin Endocrinol Metab 2016;101(11):4322–4328. doi:10.1210/jc.2016-1858, PMID:27754722.