



Review Article

Food and medicine homology substances in cancer treatment: a focus on resveratrol against gastrointestinal tumors

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Abstract: The concept of food and medicine homology is rooted in traditional Chinese medicine, which emphasizes the significance of substances having both nutritional and therapeutic capabilities. According to these characteristics, food and medicine homology substances may offer an innovative way of treating diseases. Cancer, a global disease with high mortality rates, poses considerable hurdles due to the severe toxic side effects of chemotherapy, which significantly reduce patient quality of life. As a result, there is an urgent need to investigate cancer treatments that have low toxicity and side effects. The use of food and medicine homology substances in cancer prevention and treatment has introduced promising prospects in this domain. Resveratrol, a compound derived from edible plants, exhibits significant anti-tumor action while being less toxic and causing fewer adverse effects. This review describes the use of resveratrol in treating gastrointestinal tumors and emphasizes the significance of food and medicine homologous compounds in tumor disease research. The effect and molecular mechanism of resveratrol to inhibit esophageal, gastric, pancreatic, liver, and colorectal cancer is emphasized. Several significant clinical trials of resveratrol targeting gastrointestinal cancers were also incorporated. This review delineates the current status and future potential of food and medicine homology in tumor diseases.

Keywords: food and medicine homology; gastrointestinal tumor; resveratrol; anti-tumor activity; molecular mechanism

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1 Introduction

1.1 Gastrointestinal tumors

Gastrointestinal tumors are some of the most common malignancies in the world, and they can exhibit a range of tropisms affecting the stomach, esophagus, colorectal region, pancreas, and hepatobiliary system in specific patients^[1-3]. These tumors are frequently associated with elevated morbidity and mortality rates, resulting in a bleak outlook for patients. The advancement of novel medical technology has enhanced the understanding of gastrointestinal cancers through investigations of their gene expression profiles, the molecular mechanisms regulating their growth, and their efficient identification and treatment^[4-8]. A range of approaches for gastrointestinal tumor management are now available, including surgery, radiotherapy, and pharmacotherapy^[9-13]. However, the study of therapeutic

options that can treat gastrointestinal tumors with low toxicity and side effects remains an essential approach to improving the quality of life of affected patients (Fig. 1).

1.2 Food and medicine homology in cancer treatment

The food and medicine homology herb is an essential component of traditional Chinese medicine, emphasizing the integrated and intertwined nature of nutritional and pharmacological properties^[14,15], exhibiting remarkable efficacy in treating diverse ailments^[16-18]. Consistent with this concept, many studies throughout the globe have probed the value of food and medicine homology substrates as candidates for the development of anticancer therapies^[19]. Although this endeavor holds significant potential, research on food and medicine homology products is still developing, highlighting the necessity for additional studies to elucidate the efficacy of these compounds in cancer management^[20].

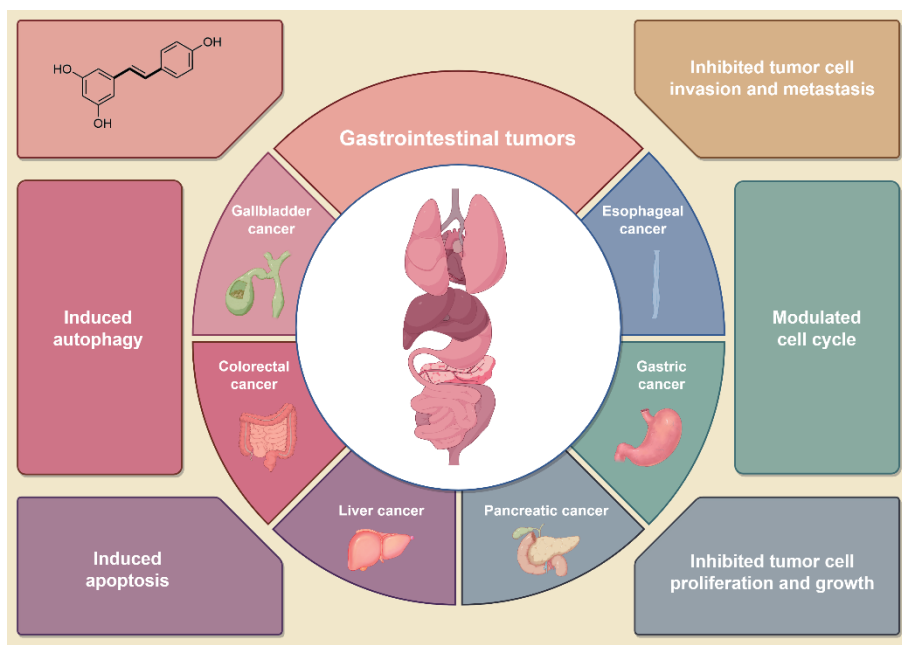


Figure 1 Effect and mechanism of resveratrol against gastrointestinal neoplasms.

1.3 Resveratrol

Resveratrol was first isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1939 by Takaoka, a polyphenol member of the stilbene family. Resveratrol is a naturally occurring compound found in various plant species and is particularly abundant in nutritionally rich foods such as grapes, peanuts, blueberries, cranberries, purple grapes, and fruit juices. It is primarily sourced from 34 plant families, encompassing approximately 100 species^[21]. Resveratrol extraction typically involves using various plant parts, including roots, stems, leaves, flowers, fruits, and seeds. In grape plants, resveratrol predominantly accumulates in the rhizomes and roots, with its concentration reaching its peak between January and September, followed by a subsequent decline^[22]. Moreover, grape skins act as a significant reservoir for resveratrol levels during the ripening process. Numerous investigations indicated that the distribution of resveratrol in this species is diverse, with elevated concentrations in the roots and rhizomes. In contrast, the leaves and vines contain comparatively lower levels^[23]. Red wine is the most notable source of resveratrol, as the red grape skins from which it is derived contain concentrations as high as 50–100 µg/g. Resveratrol exists in the form of both *cis* and *trans* isolates, the latter exhibiting superior bioactivity such that they are the primary targets for research focused on this polyphenol. In prior reports, Resveratrol has exhibited a wide range of anti-inflammatory, antitumor, and antioxidant activities^[24–27].

The application of resveratrol as a nutritional supplement is constrained by its low oral bioavailability, poor aqueous solubility (<0.05 mg/mL), and considerable chemical instability^[28]. Upon oral administration, approximately 75% of a 25 mg dose of resveratrol is absorbed^[29]. Previous research has documented the absorption or uptake of resveratrol by various cell types^[30,31]. Nevertheless, despite its high absorption rate, its bioavailability remains limited^[32]. *In vivo* studies have shown that resveratrol is detectable in the bloodstream within 30–60 min post-ingestion, suggesting efficient absorption from the gastrointestinal tract^[32]. Resveratrol is swiftly metabolized in the small intestine *via*

sulfation and glucosylation pathways. Furthermore, gut microbiota in the large intestine metabolizes these compounds, producing dihydro resveratrol, laurin, and 3,4'-dihydroxytrans-stilbene^[33]. The pharmacokinetic characteristics of resveratrol suggest that its metabolites may significantly influence gut health. Resveratrol-3-*O*-sulfate has been shown to promote the development of advantageous gut microbiota, including *Lactobacillus reuteri*, and to enhance intestinal barrier integrity^[34]. These findings suggest that resveratrol metabolites may significantly contribute to its overall health benefits, particularly concerning gut microbiota composition and intestinal health.

Chronopharmacokinetic investigations have demonstrated that administering resveratrol in the morning increases bioavailability^[35]. Moreover, when resveratrol is ingested concomitantly with food, as opposed to under fasting conditions, its absorption is delayed^[36]. Resveratrol and its metabolites are predominantly excreted *via* urine and feces, with research demonstrating a substantial proportion of the ingested dose is eliminated through these pathways^[37]. However, it is essential to consider the possible toxicity of resveratrol and its metabolites. Despite being usually regarded as safe, large dosages of resveratrol can have negative consequences, such as gastrointestinal problems and drug interactions^[38]. The absorption, distribution, metabolism, excretion, and toxicity of resveratrol are intricate processes affected by multiple factors, including the compound's molecular structure and additional dietary constituents. A thorough comprehension of these processes is crucial for maximizing the therapeutic efficacy of resveratrol while mitigating related health concerns^[39,40]. While resveratrol shows promise as an anticancer agent, it's important to note that its bioavailability in humans is relatively low and novel delivery systems to improve its absorption and efficacy *in vivo* are of a great interest. It needs to be mentioned some studies identified potential toxicological effects of resveratrol in both *in vitro* and *in vivo* models^[41,42]. High-dose administration of resveratrol may inhibit cytochrome P450 enzymes systemically, and its interactions with certain pharmaceuticals could reduce their effectiveness, posing potential risks^[43].

Remarkably, resveratrol can sustain its anticancer effectiveness

as a compound similar to food and medication while exhibiting low toxicity and few adverse effects. Thorough investigations on the impact of resveratrol on gastrointestinal malignancies could enhance the existing scientific knowledge regarding the utilization of food and medicine homology substrates for tumor therapy^[44-48]. There are currently five key areas of research focused on applying resveratrol for the management of gastrointestinal tumors: 1) studies of the ability of resveratrol to prevent tumor development^[49-52]; 2) studies of the ability of the *in vitro* and *in vivo* anti-tumor effects of resveratrol and its underlying mechanisms; 3) research focused on the anti-tumor activity of resveratrol derivatives; 4) research focused on the potential ability of resveratrol to enhance chemo- and radiotherapeutic efficacy; and 5) the use of nano-drug delivery technologies to augment the bioavailability of resveratrol or to enhance its sustained release (Fig. 2).

This review provides a comprehensive overview of the effects of resveratrol as a pharmacological tool for managing gastrointestinal tumors and the underlying molecular mechanism. The impact of resveratrol on particular tumor types (esophageal, gastric, pancreatic, liver, and colorectal cancers (CRC)) is examined, alongside a comprehensive analysis of the targets and pathways associated with resveratrol's capacity to impede tumor cell proliferation, growth, invasion, and metastasis, enhance autophagy, modulate cell cycle progression, and regulate apoptotic cell death. Several significant clinical trials of resveratrol targeting gastrointestinal cancers were also incorporated. Finally, this review elucidates resveratrol's current status and limitations in anti-digestive tract tumor research while providing a concise

overview of its developmental prospects (Fig. 3). The possible therapeutic benefit of food and medicine homology substances in treating cancers is also briefly reviewed. It is important to acknowledge that, although biliary tract tumors represent a significant subset of gastrointestinal malignancies, this review does not specifically address the role of resveratrol in their treatment due to the paucity of research in this area.

2 Resveratrol inhibits esophageal cancer progression

Esophageal cancer (EC) is the eighth most prevalent and sixth deadliest cancer globally^[53,54]. EC cases are primarily classified into two subtypes based on their epidemiological, histopathological, and molecular features, including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) cases^[55,56]. The most popular methods for managing EC are still surgery and chemotherapy, despite the development of more sophisticated treatment plans in recent years. Resveratrol has been shown in numerous studies to limit proliferative, invasive, and metastatic development while promoting autophagic and apoptotic activity, preventing EC progression both *in vitro* and *in vivo*^[57,58].

2.1 Resveratrol prevents EC onset

While an early study from 2022 published by Li *et al.*^[59] demonstrated the ability of resveratrol to inhibit *N*-nitrosomethylbenzylamine-induced esophageal tumorigenesis in a rat model system. Still, relatively little work in the intervening

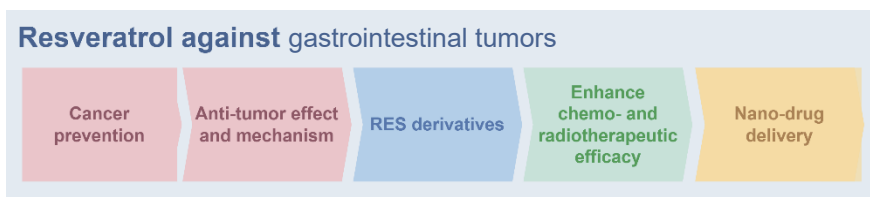


Figure 2 Application of resveratrol in gastrointestinal tumors.

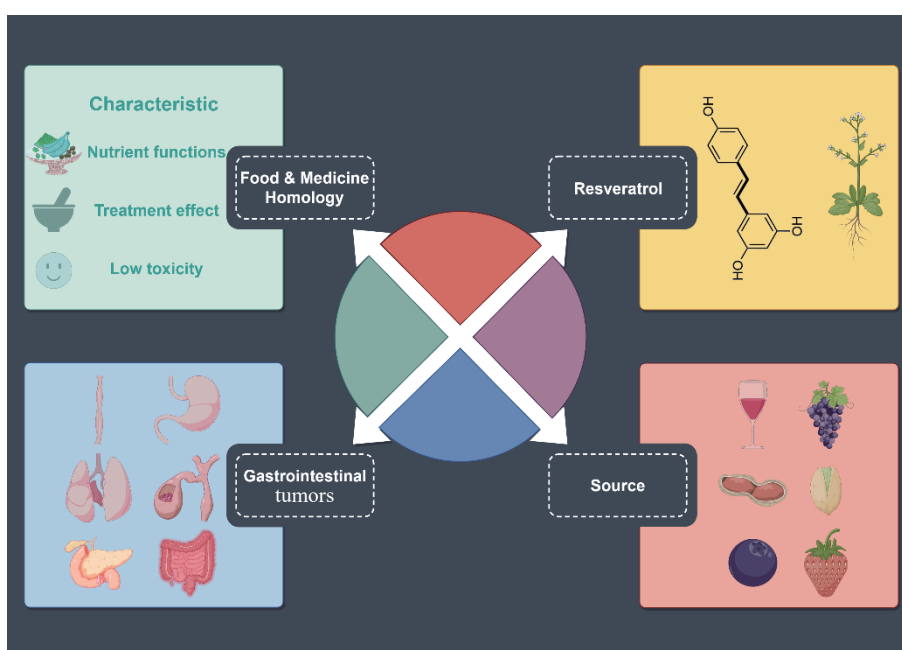


Figure 3 Food and medicine homology substances in cancer treatment.

years has probed the ability of resveratrol to protect against EC. In 2009, Martin *et al.*^[60] performed a long-term study of male Sprague-Dawley (SD) rats undergoing esophagoduodenostomy explored how resveratrol affects esophageal lesion progression and provided further support for its ability to limit EC growth, given that it effectively alleviated esophagitis symptoms while reducing EAC incidence.

2.2 Resveratrol suppresses ESCC development

2.2.1 Induction of apoptosis

Jin *et al.*^[61] explored the mechanisms through which resveratrol can affect ESCC cells and ultimately demonstrated its ability to dose-dependently suppress the proliferation of these cells and associated colony formation. Resveratrol treatment induced ESCC cell cycle arrest and apoptosis in the G0/G1 phase. The researchers hypothesized that regulating the epidermal growth factor receptor (EGFR) signaling pathway was responsible for these anti-cancer effects. Interestingly, short-term resveratrol treatment was linked to EGFR phosphorylation and associated signaling activity inhibition in ESCC cells. Meanwhile, prolonged therapy led to EGFR degradation, reducing nuclear and membrane-associated EGFR activity.

Song *et al.*^[62] found that resveratrol effectively inhibited *in vitro* and *in vivo* ESCC growth by suppressing proliferative activity, cell cycle arrest, and apoptotic induction. The underlying mechanism was associated with targeted inhibition of the thousand and one amino acid protein kinase 1 (TAOK1) protein kinase, which functions upstream of the MAPK signaling axis. Specifically, TAOK1 was upregulated in ESCC tumors and cell lines, and knocking it down compromised the growth of ESCC tumor cells *in vitro* and *in vivo*, whereas its overexpression yielded the opposite effect. Through a combination of molecular docking and surface plasmon resonance (SPR) analyses, the researchers demonstrated that resveratrol could directly interact with TAOK1, suppressing the growth of the TAOK1-overexpressing HEG18 and LEG269 patient-derived xenograft (PDX) tumor models in mice.

Li *et al.*^[63] found that resveratrol was capable of dose- and time-dependently inhibiting the growth of the human EC cell line Eca109 while promoting the apoptotic death of these cells. In transmission electron microscopy analyses of these cells, clear evidence of apoptotic induction was evident, including cytoplasmic vacuolation and chromatin condensation. Consistent with these features, qPCR and flow cytometry approaches revealed Bax upregulation and reduced survivin protein levels in these cells, consistent with ongoing apoptotic signaling.

Tang *et al.*^[64] determined that resveratrol could induce the apoptotic death and autophagic activation of ESCC cells while inhibiting their growth through mechanisms independent of traditional AMPK/mTOR pathway activation. They also noted p53 upregulation in this experimental context, suggesting that it may play a role in resveratrol-induced ESCC cell apoptosis.

2.2.2 Inhibition of migration and invasion

Lin *et al.*^[65] documented the ability of resveratrol to suppress the expression of a distegrinin and a metalloprotease 9 (ADAM9), thereby limiting ESCC cell migration and viability. At the molecular level, this activity was attributed to the ability of resveratrol to enhance the degradation of ADAM9 mediated by the ubiquitin-proteasome without any corresponding changes in its transcriptional expression. The authors of this study also

highlighted the excellent safety profile of resveratrol when administered orally.

2.3 Resveratrol inhibits EAC development

Dhir *et al.*^[66] revealed that resveratrol dose-dependently limited the viability and growth of three EAC cell lines (OE33, OE19, and FLO-1) through apoptotic induction. The underlying mechanisms coincided with altered reactive oxygen species (ROS) levels and the protein level expression of Bcl-2, consistent with the importance of Bcl-2-Caspase pathway activation in this context.

2.4 Preliminary summary

EC remains a pressing threat to global public health, and resveratrol has emerged as an increasingly promising antitumor agent. Resveratrol can inhibit EC cell growth by modulating signaling activity, cell cycle arrest, and apoptotic induction. Through its ability to directly target EGFR signaling, resveratrol can induce cell cycle arrest and apoptotic death in ESCC cells. TAOK1 has also been established as an essential signaling molecule, and interactions between resveratrol and TAOK1 are closely related to the impairment of ESCC cell proliferation. These apoptotic effects of resveratrol treatment are potentiated at least in part through autophagic inhibition, highlighting innovative opportunities for EC treatment. Resveratrol has also been shown to offer utility as a treatment for EAC, suppressing EAC cell proliferation through AMPK signaling pathway activation while activating other signaling circuits within these tumor cells to alter their molecular and immunomodulatory characteristics.

Several barriers to the use of resveratrol for EC treatment remain, including a need for additional research to clarify the optimal dosages for patient treatment and the underlying mechanisms of action. Given the complex nature of EC, additional studies aimed at synergistically combining resveratrol and other treatment options are a particularly promising avenue for further research. The further advancement of the genetic and molecular mechanisms that underlie EC will aid in the more extensive application of resveratrol by identifying novel therapeutic targets. On the whole, resveratrol holds promise for EC treatment, and further studies aimed at elucidating the associated mechanisms of action and clinical prospects have the potential to provide patients with hope for better treatment outcomes. Additionally, investigating potential synergistic effects between resveratrol and conventional chemotherapeutic agents could lead to more effective combination therapies for EC.

3 Resveratrol inhibits the progression of gastric cancer

Gastric cancer (GC) is another common form of cancer that is primarily treated using surgical and chemotherapeutic methods^[67-69]. Plant-derived natural compounds, including curcumin^[70], berberine^[71], and resveratrol^[72], have all been shown to exhibit anticancer activity in the management of GC^[73]. Resveratrol has been demonstrated to inhibit GC cell invasion and metastasis while inducing apoptotic death.

This section offers a detailed overview of recent studies exploring how resveratrol affects GC cells, focusing on how it suppresses invasive or metastatic growth and induces apoptosis. The discussion focuses on the related mechanisms of action and the opportunities and barriers associated with the clinical use of resveratrol, offering insight into new approaches to managing GC.

3.1 Resveratrol inhibits the invasion and metastasis of GC cell

The epithelial-mesenchymal transition (EMT) process is central to the enhancement of progressing tumor cell migration as they shed their epithelial characteristics in favor of a mesenchymal phenotype^[74,75]. EMT induction is consistently linked to improved tumor cell migration from primary sites to distant tissues, thereby facilitating malignant progression^[76,77].

Gao *et al.*^[78] found that resveratrol could inhibit Hedgehog (Hh) signaling and EMT induction in the SGC-7901 GC cell line, limiting the ability of these cells to migrate and invade. These researchers noted that resveratrol treatment was associated with reductions in GLI family zinc finger 1 (Gli-1), Snail, and *N*-cadherin levels while increasing E-cadherin expression. Of these proteins, Gli-1 is closely related to Hh signaling, whereas Snail, E-cadherin, and *N*-cadherin are related to EMT induction.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been demonstrated to offer value as a prognostic biomarker in GC that is highly expressed in the context of GC distant metastasis^[79]. Yang *et al.*^[80] found that resveratrol suppressed human GC cell invasion and migratory activity by affecting MALAT1 and disrupting EMT induction. In CCK-8 assays, resveratrol was demonstrated to suppress SGC7901 and BGC823 GC cell viability, with similar effects on non-malignant GES1 gastric epithelial cells in a dose- and time-dependent fashion. qPCR analyses also demonstrated that resveratrol treatment was associated with significantly reduced MALAT1 expression within BGC823 cells. Silencing MALAT1 was a similarly effective means of inhibiting the survival, growth, migration, and EMT activity of these cells.

The tumor microenvironment (TEM) plays a crucial role in tumor progression^[81,82], with mesenchymal stem cells (MSCs), in particular, functioning as vital TEM components related to tumor metastasis^[83,84]. Yin *et al.*^[85] determined that GC-derived MSCs can enhance GC cells' metastasis and EMT activity due to their ability to secrete interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and vascular endothelial growth factor (VEGF). In contrast, resveratrol was sufficient to inhibit this process. Moreover, resveratrol reversed the increases in *N*-cadherin, vimentin, and α -smooth muscle actin (α -SMA) protein levels noted in GC-MSC-induced GC cells while additionally antagonizing the Wnt/ β -catenin pathway activity induced in these cells by GC-MSCs, as demonstrated by decreased nuclear β -catenin transport and reduced β -catenin, CD44, and Cyclin D3 expression.

The Hippo pathway plays an essential role in the regulation of the proliferation and differentiation of cells^[86]. Hippo-YAP pathway modulation in GC can favor EMT induction or metastatic growth^[87]. Deng *et al.*^[88] posited that resveratrol can partially suppress GC cell EMT through Hippo-YAP signaling inhibition. Resveratrol led to the dose- and time-dependent suppression of SGC-7901 cell invasion, migration, and growth. It also inhibited EMT induction in response to TGF- β 1, reversing morphological changes and promoting E-cadherin upregulation with vimentin, *N*-cadherin, and Snail downregulation at the transcript and protein levels. Resveratrol is thus capable of effectively inhibiting transforming growth factor- β 1 (TGF- β 1)-induced EMT activity. The authors also utilized a cell line-derived xenograft (CDX) model to confirm the ability of resveratrol to counteract GC growth through these mechanisms.

Rojo *et al.*^[89] reported that the dose-dependent suppression of

AGS and MKN45 GC cell activity and invasion in response to resveratrol. Specifically, ELISAs demonstrated that resveratrol treatment was associated with the enhancement of superoxide dismutase (SOD) activity, the attenuation of DNA binding by nuclear factor κ -B (NF- κ B), and the suppression of heparinase activity, ultimately resulting in reduced GC cell survival and invasion.

3.2 Resveratrol induces GC cell apoptosis

In 2005, Zhou *et al.*^[90] used human GC-derived xenograft model systems to begin exploring how resveratrol can inhibit GC growth. They ultimately demonstrated the induction of apoptosis in resveratrol-treated cells, as evidenced by chromatin condensation and nuclear fragmentation. Both immunohistochemistry and RT-PCR analyses supported the ability of Bcl-2 downregulation and Bax upregulation to facilitate apoptotic induction in these cells.

Network pharmacology, molecular docking, bioinformatics, and *in vitro* experiments were used to demonstrate the inhibition of AGS cells^[91]. Differential expression analyses of essential target genes in GC tissue samples revealed decreased fos proto-oncogene (FOS) protein levels and higher MMP-9 levels relative to normal tissues. In molecular docking analyses, resveratrol was found to bind these two proteins strongly, and this was further supported by experimental evidence demonstrating the ability of resveratrol to target FOS and MMP-9 to suppress migratory, invasive, and proliferative growth through S-phase arrest and apoptotic induction. In qPCR analyses, resveratrol inhibited FOS expression at the mRNA while upregulating MMP9.

Dong *et al.*^[92] Additionally, it confirmed the ability of resveratrol to suppress GC growth *in vivo* in a xenograft model system, demonstrating that it can modulate PI3K/Akt/P53 signaling to exert these effects. Through network pharmacology analyses, the authors identified AKT serine/threonine kinase 1 (AKT1), tumor protein P53 (TP53), Jun proto-oncogene (JUN), estrogen receptor 1 (ESR1), and MAPK14 as crucial targets of such treatment, while functional enrichment analyses noted a role for the PI3K/Akt/P53 pathway in this activity. Resveratrol-mediated inhibition of AGS and HGC-27 cell proliferation and its ability to promote apoptotic death were significantly reversed when LY294002 was used to block PI3K-Akt signaling.

Abnormal Wnt/ β -catenin pathway activation is closely linked to human tumor development^[93]. When abnormally activated, β -catenin that has not been phosphorylated or degraded undergoes nuclear translocation and interacts with specific transcription factor 4 (TCF-4) domains, generating transcriptional complexes associated with the induction of tumorigenesis^[94]. In GC, runt-related transcription factor 3 (RUNX3) forms a ternary complex with TCF-4 and β -catenin, impairing the ability of Wnt target gene promoters to interact with this complex and thereby inhibiting canonical Wnt signaling^[95]. Liu *et al.*^[96] found that resveratrol can inhibit GC progression by altering caudal type homeobox 2 (CDX2) and RUNX3 expression while modulating β -catenin/TCF4 signaling activity. RUNX3 and CDX2 expression was positively correlated in GC tissues, whereas negative correlations with β -catenin and TCF-4 levels were noted. *In vitro* analyses revealed the ability of resveratrol to suppress cellular proliferative, invasive, and migratory growth together with apoptotic induction. At the mechanistic level, resveratrol was demonstrated to upregulate RUNX3 and Bax while downregulating β -catenin, TCF-4, and Bcl-2.

Yang and Xia^[97] noted the ability of resveratrol to suppress GC

cell invasive, proliferative, and migratory growth through MALAT1/miR-383-5p/DDIT4 pathway regulation, inducing apoptotic death. MALAT1 has been established as a promoter of tumor cell malignancy, and resveratrol can reduce MALAT1 levels within cells, increasing the rate of apoptosis. MALAT1 has been demonstrated to partially function by targeting miR-383-5p, which inhibits DNA damage inducible transcript 4 (DDIT4). Inhibiting MALAT1 and miR-383-5p expression can abrogate the antitumor benefits of resveratrol.

Su *et al.*^[98] explored miR-155-5p upregulation in GC cell and tumor tissue samples, revealing that resveratrol could inhibit GC cell proliferative activity while inducing apoptotic death *via* the modulation of miR-155-5p expression. MiR-155-5p mimic transfection increased claudin 1, myelocytomatosis viral oncogene homolog (c-Myc), cyclin D1, and Bcl-2 levels within cells while lowering caspase-3 levels, whereas resveratrol treatment reversed these changes in miR-155-5p mimic transfected cells.

Yang *et al.*^[99] found the ability of resveratrol to induce SGC-7901 cell apoptosis *via* mitochondrial pathway activation. After treatment with resveratrol, cells exhibited lysed poly ADP-ribose polymerase (PARP) and activated caspase-3. Decreases in mitochondrial membrane potential were also observed in these cells, together with mitochondrial cytochrome C release into the cytosol and an increased Bax/Bcl-2 ratio in these cells, offering further support for resveratrol as an anticancer drug.

Wu *et al.*^[100] found that resveratrol dose- and time-dependently suppressed SGC-7901 cell viability through the induction of apoptosis, with flow cytometry also revealing the induction of S-phase cell cycle arrest in these GC cells. Pro-apoptotic Bax, cleaved caspase-3, and cleaved caspase-8 protein levels also dose-dependently increased in response to resveratrol, whereas there was a corresponding decline in anti-apoptotic Bcl-2 levels.

Survivin is an anti-apoptotic protein overexpressed in many cancers that is often related to a poor prognosis and aggressive tumor growth. Liu *et al.*^[101] found that resveratrol targets Survivin in SGC7901 cells to induce their apoptotic death, suppress proliferation, and disrupt normal progression through the cell cycle such that a more significant proportion of treated cells were observed in the G0/G1 phase. In contrast, G2/M and S-phase cells were less common.

3.3 Preliminary summary

As the studies above demonstrate, resveratrol can effectively suppress GC tumor development. Network pharmacology and bioinformatics studies have unveiled an array of resveratrol-related targets and signaling pathways. For instance, resveratrol can limit CDX-deficient GC cell growth by modulation of β -catenin/TCF4 signaling *via* RUNX3 and CDX2. Resveratrol can also suppress GC cell migratory, invasive, and proliferative activity *via* the MALAT1/miR-383-5p/DDIT4 axis, ultimately inducing apoptosis.

PI3K/Akt/P53 signaling is central to the development of GC, and resveratrol can affect this pathway to impair GC cell proliferation and apoptosis. Resveratrol can also downregulate miR-155-5p, thereby limiting GC cell malignancy while inducing the mitochondrial apoptosis pathway within the SGC7901 GC cell line.

There has also been much research interest focused on the roles that long noncoding RNAs (lncRNAs) play in this pathological context. H19 is a lncRNA that can enhance the ability of resveratrol to inhibit GC cell proliferation and migration through activity related to endoplasmic reticulum stress. MALAT1 is also closely linked to EMT induction in GC cells, and resveratrol

suppresses the expression of MALAT1 to limit the ability of these cells to engage in invasive and migratory activity. As such, lncRNAs are closely related to the biological features of GC cells and should be studied to inform the design of therapeutic strategies.

There are still several barriers to the resveratrol-based treatment of GC. For one, the underlying mechanisms it functions warrant additional *in vivo* confirmation, and studies of how it can synergize with other drugs or therapeutic strategies are necessary. In addition, the complex and diverse nature of GC tumors underscores the importance of designing individualized treatment approaches. Approaches to improving resveratrol bioavailability and stability will also be invaluable for enhancing its therapeutic efficacy. Lastly, advances in precision medicine will fuel the combination of genomic, proteomic, and other approaches to devise more accurate methods for GC treatment.

4 Resveratrol inhibits pancreatic cancer progression

Pancreatic cancer (PC) is a deadly form of cancer, the early symptoms of which are often overlooked given their subtlety such that patients tend to be diagnosed with advanced disease^[102, 103]. Key factors involved in PC onset and progression include a range of dietary and lifestyle factors^[104]. Given its diverse biological activities and status as a natural polyphenolic compound, resveratrol has attracted substantial interest in the PC research space^[105]. This section offers a detailed overview of the use of resveratrol in treating PC, its mechanisms of action, and its prospects for clinical application. This discussion includes a critical examination of current challenges in the field and future directions for research to help inform PC treatment.

4.1 Resveratrol induces the apoptosis of PC cells

Caspases 3 and 7 orchestrate apoptotic programmed cell death within cells^[106], cleaving distinct substrates to promote chromatin fragmentation, membrane blebbing, cellular contraction, and eventual degradation. This leads to the eventual formation of membrane-coated vesicles apoptotic bodies^[107].

Proteins in the Bcl-2 family are vital to apoptotic induction, and they are classified into three subgroups according to their structural and functional properties^[108]. The Bcl-2 subfamily is composed of anti-apoptotic factors, including Bcl-2 and Bcl-xl; the Bax subfamily includes the pro-apoptotic Bax and Bak proteins, and the BH3 subfamily consists of the pro-apoptotic Bid and Bad proteins, which also harbor a BH3 domain required for apoptotic induction. The control of an appropriate balance of these proteins is vital to facilitate cellular survival^[109, 110]. When these different proteins interact, they can activate proteolytic caspases, thereby damaging the cytoskeleton and organelles and promoting DNA degradation^[111]. Several apoptosis-related targets of resveratrol have been documented to date, including MAPK, CD95, p53, Bcl-2, and Bax.

Bcl-2 can strongly regulate apoptotic induction, and suppressing the expression thereof can thus readily trigger tumor cell death^[112, 113]. MiR-21 has been repeatedly demonstrated to impair apoptotic activity through its ability to decrease Bcl-2 levels^[114]. Liu *et al.*^[115] found that resveratrol is capable of inducing PC cell apoptosis by altering Bcl-2 levels in a miR-21-mediated fashion. Resveratrol can also dose-dependently inhibit PANC-1, CFPAC-1, and MIA Paca-2 cell growth, and significantly lower miR-21 levels were noted by qPCR in these cells following

resveratrol exposure, leading to subsequent Bcl-2 downregulation. Overexpressing miR-21 can reverse such Bcl-2 downregulation and rescue this resveratrol-induced apoptotic death.

Caspase-3 is a cysteine-aspartate protease vital for apoptotic induction that is often used as a biomarker of apoptosis^[116]. Zhou *et al.*^[117] found that resveratrol activated caspase-3 to promote the apoptotic death of Capan-2 and col357 PC cells in a dose-dependent fashion while having little effect on normal HPDE pancreatic cells. These researchers also observed the ability of resveratrol to activate the MAPK-Erk pathway and induce the accumulation of p53 through a mechanism closely linked to apoptosis.

Ratajczak *et al.*^[118] explored the pro-apoptotic effects of resveratrol on a range of human PC lines (EPP85-181P, EPP85-181RNOV, and AsPC-1), ultimately determining that it is capable of dose-dependently inducing apoptosis in these cells. The most pronounced increases in early apoptotic marker levels were noted in EPP85-181P cells, while they were only marginally increased in AsPC-1 cells. Immunocytochemical staining efforts further confirmed the pro-apoptotic effects of resveratrol, as evidenced by increased Bax and Caspase-3 protein expression and Bcl-2 downregulation. In addition to its ability to promote Bax upregulation, resveratrol can upregulate VegF-B to act as a tumor promoter^[119]. However, current evidence suggests that its antitumor effects outweigh any potential risk of oncogenic activity.

Kotha *et al.*^[120] found that resveratrol could activate apoptotic signaling in PC cell lines with constitutive signal transducer and activator of transcription 3 (STAT3) activity (Colo-357 and PANC-1 cells), but it had little effect on cells that lack such STAT3 activity. Mechanistically, they determined that resveratrol can suppress Src tyrosine kinase activity and downstream STAT3 signaling activity within these cells. Consistent with these findings, Annexin V staining revealed the ability of resveratrol to selectively induce the apoptosis of v-Src-transformed mouse fibroblast (NIH3T3v-Src) exhibiting constitutive Stat3 activity. In contrast, the same was not true in normal NIH3T3 fibroblasts. At the molecular level, resveratrol was determined to affect STAT3 signaling by suppressing cyclin D1, Bcl-xl, and Mcl-1 expression.

Intratumoral anaerobic glycolysis leads to the acidification of the TME, which contributes to aggressive tumor growth^[121,122]. Shamim *et al.*^[123] noted that resveratrol could inhibit growth while enhancing apoptosis induced by the fragmentation of nucleosomal DNA in Capan-2 and PANC-28 PC cells under lower pH conditions. Apoptosis assays confirmed that significantly greater Capan-2 and PANC-28 apoptosis was evident at a pH of 6.5 or 7.0 relative to a pH of 7.5.

4.2 Resveratrol inhibits PC cell growth and proliferation

In 2002, Ding *et al.*^[124] documented the ability of resveratrol to inhibit human PC cell proliferation (PANC-1 and AsPC-1) cells in a dose- and time-dependent manner. It was further found to lead to the accumulation of cells in the S phase while reducing their accumulation in the G0/G1 phase. However, no corresponding analyses were performed to clarify the underlying mechanisms responsible for these results.

Qian *et al.*^[125] found that resveratrol could delay PC development in the LSL-Kras^{G12D/+}; Pdx1-Cre (KC) mouse model of spontaneous pancreatic precancerous lesion formation due to its ability to inhibit NF- κ B activation. This effect was linked to the ability of resveratrol to prevent low-grade lesions from progressing into high-grade lesions rather than through the delay of late pancreatic acinar cell transformation throughout oncogenesis. The

resveratrol pretreatment of KC mice with chronic pancreatitis can mitigate inflammatory activity and the formation of precancerous pancreatic lesions. In addition to the evidence that resveratrol can suppress NF- κ B signaling activity, it was also shown to limit ERK and STAT3 activation associated with precancerous lesions in KC mice. STAT3 has been regarded as an alternative activating pathway in suppressing MEK/ERK signaling that may be involved in PC chemoresistance^[126]. As resveratrol can simultaneously suppress ERK/STAT3 and NF κ B activation, it may offer value as a chemosensitizing agent that can combat PC with a high degree of efficacy extending beyond its preventative benefits.

Pereira *et al.*^[127] further observed the ability of resveratrol to prevent the CCK-induced destruction of pancreatic tissue through the downregulation of NF- κ B. The authors noted reduced premature activation and subsequent necrosis of trypsin in pancreatic cells following resveratrol treatment, with both of these activities being important pathological events that arise early during pancreatitis and PC development.

Roy *et al.*^[128] found that resveratrol can inhibit pancreatic tumor growth by inhibiting forkhead box O (FOXO) transcription factor activation. Specifically, resveratrol inhibited PC cell viability and colony formation, induced caspase-3 activation, and promoted apoptosis while inhibiting cyclin D1 expression and promoting p21/CIP1 and p27/KIP1 upregulation to promote cell cycle arrest. Resveratrol was further shown to stimulate the translocation of FOXO transcription factors to the nucleus, promote their binding to DNA, and enhance associated transcriptional activity through mechanisms attributed to PI3K/AKT and MEK/ERK pathway inhibition. These researchers also used a CDX model and revealed that resveratrol was sufficient to significantly suppress the growth of pancreatic tumors in mice through the suppression of ERK, PI3K, AKT, FOXO1, and FOXO3a phosphorylation while increasing apoptosis rates and FOXO target gene expression. Combined inhibition of the ERK and AKT signaling pathways thus appears to be closely associated with FOXO transcription factor activation, thereby mediating the antitumor effects of resveratrol when used to treat pancreatic tumors.

Mo *et al.*^[129] observed the ability of resveratrol to modulate Hh pathway signaling in a dose- and time-dependent fashion to limit PC cell proliferation. These effects coincided with significant reductions in Gli1, Ptc1, CCND1, and Bcl-2 levels in resveratrol-treated PC cells, while Gli1 gene transfection led to Ptc1, CCND1, and Bcl-2 upregulation that was suppressed by resveratrol. As such, the ability of resveratrol to suppress proliferative activity may be related to the Hh/Gli1 pathway-mediated downregulation of CCND1 and Bcl-2.

Jiang *et al.*^[130] noted the ability of resveratrol to suppress PANC-1 and SW1990 cell proliferative, migratory, and invasive growth through the downregulation of ryanodine receptor type 2 (RyR2). Resveratrol has subsequently been shown to achieve these inhibitory effects by upregulating phosphatase and tensin homolog (PTEN), a critical tumor suppressor gene, within PC cells, thus limiting PC progression.

Mo *et al.*^[129] demonstrated the ability of resveratrol to significantly inhibit PC cells under chronic stress conditions in a dose-dependent manner. β 2-Adrenergic receptor (ADRB-2) is a sympathetic nervous system receptor activated under chronic stress conditions, contributing to the formation and progression of tumors^[131]. Resveratrol can inhibit tumor cell growth by reducing ADRB-2 expression while limiting the expression of hypoxia inducible factor 1 α (HIF-1 α), which plays a central role in tumorigenesis.

4.3 Suppression of invasion and metastasis

Experimental evidence suggests that resveratrol can modulate EMT-associated processes *via* the PI3K/Akt/NF- κ B signaling axis to limit tumor proliferation and malignant growth^[132]. At the molecular level, resveratrol treatment was found to dose-dependently suppress PC cell expression of the MMP-2 and MMP-9 members of the extracellular matrix-degrading matrix metalloproteinase (MP) family. Resveratrol has also been shown to suppress PC cell migration induced by TGF- β and associated morphological changes, inhibiting the phosphorylation of the metastasis-related Akt and NF- κ B proteins.

Hypoxia is established as an essential driver of EMT induction through the modulation of EMT-related signaling pathways, the activation of related transcription factors, and the modulation of associated miRNA regulatory networks^[133]. Intratumoral hypoxia is also closely associated with enhanced invasion, angiogenic activity, and distant metastatic growth^[134]. HIF-1 is the central transcription factor responsible for controlling signaling within tumor cells under hypoxia conditions, and it consists of the HIF-1 α and HIF-1 β subunits^[135].

Li *et al.*^[136] explored the effects of resveratrol on HIF-1 α signaling to inhibit PC cell invasion and migration. After demonstrating the suppression of both such malignant activities through *in vitro* Transwell and wound healing assays, they determined that the underlying mechanisms were linked to the protein level downregulation of HIF-1 α in BxPC-3 and PANC-1 cells in the presence of hypoxia, without any corresponding mRNA level changes. Moreover, resveratrol was found to downregulate the Hh pathway proteins smoothened (SMO), sonic hedgehog (SHH), and GLI1, consistent with the downregulation of this activated pathway under hypoxic conditions. This is notable given the importance of this pathway in hypoxia-mediated tumor cell EMT induction and invasion. Resveratrol was additionally able to suppress hypoxia-related ROS production in this experimental setting.

Molecular docking and molecular dynamics simulation studies performed by Srivani *et al.*^[137] have demonstrated that resveratrol can bind HIF-1 α , potentially inhibiting its function to limit PC progression. Specifically, resveratrol was found to hydrophobically interact with the HIF-1 α Thr288 and Tyr276 residues, leading to the observed inhibitory effects.

PC tumors generally exhibit a highly hypoxic TME, owing in large part to extensive pancreatic stellate cell (PSC)-related fibrosis. PDAC cases are characterized by the activation of PSCs in response to such intratumoral hypoxia, leading to enhanced invasive growth^[138]. Under these conditions, PSCs can promote fibrosis while additionally secreting chemokines and cytokines that promote invasion, development, and metastasis^[139]. Suppressing such hypoxia-induced PSC activation is thus vital for effectively inhibiting progressive tumor growth.

Xiao *et al.*^[140] explored how resveratrol affects hypoxia-mediated PC progression. They ultimately found that *in vitro*, resveratrol could inhibit the activation of PSCs under hypoxic conditions owing to α -SMA and HIF-1 α downregulation. Such treatment also reversed the enhanced PSC-mediated secretion of IL-6, VEGF-A, and SDF-1, usually evident under hypoxic conditions, limiting their ability to promote PC cell invasion. Resveratrol also suppressed EMT induction in Mia Paca-2 and PANC-1 cells under hypoxic conditions. At the same time, *in vivo*, it limited the desmoplastic reaction in KPC model mice *via* the suppression of VEGF-A, SDF-1, and IL-6 production. These results highlight the multi-pathway mechanisms through which resveratrol limits PC

cell metastatic and invasive growth.

Epidemiological studies have highlighted the closely correlated nature of diabetes and PC, with diabetes contributing to both the risk of PC itself and related complications^[141]. Hyperglycemia can drive PC cell proliferation while enhancing the migration and invasion of these cells^[142]. ROS production is also closely linked with hyperglycemia-induced PC cell migratory and invasive growth^[143,144]. Related downstream signaling pathways include the ERK and p38 MAPK pathways, facilitating NF- κ B activation to drive migration^[145]. Cao *et al.*^[146] demonstrated that resveratrol is capable of inhibiting ROS-driven PC cell migration and invasion through the suppression of ERK and p38 MAPK signaling, inhibiting hyperglycemia-induced PANC-1 cell invasion, migration, and proliferative growth while simultaneously reducing the generation of H₂O₂ and other ROS. Following resveratrol treatment, these researchers observed reduced ERK and p38 phosphorylation in response to hyperglycemic conditions. NF- κ B phosphorylation was also reversed by the addition of resveratrol.

4.4 Preliminary summary

Recent studies have demonstrated the ability of resveratrol to limit early changes associated with the transition from pancreatitis to PC, particularly in pancreatic acinar cells. Several mechanisms have been established through which resveratrol can inhibit tumor cell growth involving the ADRB-2-HIF-1 α , ERK/p38 MAPK, Hh, and PI3K/Akt/NF- κ B pathways. By suppressing these various pathways, all of which are closely involved in the formation of many pancreatic tumors, resveratrol can provide novel opportunities to manage these malignancies. It can also induce PC cell apoptotic death through processes mediated by many factors, including acidic conditions, ROS generation, miR-21 modulation, and FOXO transcription factor activation. Strikingly, several studies have noted the ability of resveratrol to exert its pro-apoptotic effects through the inhibition or downregulation of crucial proteins, including HIF-1 α and Bcl-2 family proteins.

Future studies should aim to clarify the synergistic benefits of combining resveratrol and other pharmacological agents or other therapeutic tools to combat PC more effectively. Future research should also explore the potential of resveratrol in combination with immunotherapy, as emerging evidence suggests that some natural compounds can enhance the efficacy of immune checkpoint inhibitors^[147]. Detailed mechanistic studies of how resveratrol functions, particularly concerning the intracellular signaling pathways it affects, may offer new insight into developing novel therapeutic options. Given the high mortality rates and complex pathological features associated with PC, efforts must be made to clarify how best to translate resveratrol into clinical practice, aiming to improve its safety and efficacy.

In conclusion, resveratrol holds clear value as a treatment for PC. Further efforts to elucidate the underlying mechanisms of action are predicted to inform the development of even more efficacious treatment strategies for patients with this devastating disease.

5 Resveratrol inhibits the progression of liver cancer

Liver cancer is among the most common cancers globally, and it imposes a heavy burden on public health owing to the high morbidity and mortality rates associated with it^[148,149]. Recent advances in medical technologies have fueled improvements in liver cancer diagnosis and treatment strategies^[150-152]. Conventional

therapeutic approaches, including radiotherapy and surgery, have been improved by implementing targeted therapies, immunotherapies, and cutting-edge techniques such as exosome- and nanotechnology-based treatments^[153-156]. These developments have contributed to the increasingly individualized treatment of cases of liver cancer. Nonetheless, there are still plenty of chances to increase these treatments' effectiveness, lessen their adverse effects, and increase patient survival. Another urgent and ongoing issue is choosing the best course of action for patients with advanced liver cancer. Numerous studies have demonstrated that resveratrol can induce cell cycle arrest in liver cancer and simultaneously inhibit proliferative development. Resveratrol can influence liver cancer cells' survival and apoptotic death by regulating many signaling pathways and protein targets. These pathways underscore novel prospects for formulating techniques for targeted liver cancer therapy. This section offers a critical analysis of existing research on the effects of resveratrol on liver cancer cells, emphasizing its methods of action, prospective therapeutic uses, and related problems. This review seeks to establish an evidence-based framework for forthcoming research on liver cancer treatment.

5.1 Inhibition of invasion and metastasis

5.1.1 Inhibition of HSC-related invasion and metastasis

Hepatic stellate cells (HSCs) play a crucial role in hepatocellular carcinoma (HCC) progression, promoting both tumorigenic and metastatic activities^[157,158]. HSCs can facilitate angiogenic growth in HCC through the upregulation of Gli-1, in turn stimulating ROS production and enhancing HCC cell aggression^[159]. HSCs also secrete a range of cytokines, including IL-6 and CXCR4, which contribute to the metastatic potential of HCC cells^[160].

Yan *et al.*^[161] determined that resveratrol could suppress HSC-mediated angiogenesis, ROS production, and CXCR4 and IL-6 production in HepG2 cells through a process related to Gli-1 downregulation. Intriguingly, the shRNA-mediated knockdown of Gli-1 eliminated the ability of resveratrol to inhibit ROS biogenesis and VEGF and IL-6 expression. Gli-1 thus appears to be a vital mediator of the ability of resveratrol to combat HCC growth.

5.1.2 Inhibition of HGD-related pathway invasion and metastasis

ROS can promote cellular invasion, and H₂O₂ treatment or hypoxanthine-xanthine oxidase (HX-XO) reaction-induced ROS induction can elevate cell peroxide levels^[162]. The resultant oxidative stress drives hepatocyte growth factor (HGF) upregulation, which mediates cellular mobility and helps promote cellular invasion^[163].

A study by De Lédinghen *et al.*^[164] revealed the ability of resveratrol to suppress HepG2 cell invasion *in vitro*, with subsequent studies confirming its efficacy in limiting HCC cell invasion and metastasis *via* HGF pathway targeting. The underlying mechanism is unrelated to any changes in cellular-mesenchymal epithelial transition factor (c-Met) levels as a receptor for HGF. They do not involve the disruption of HGF-induced increases in c-Met precursor synthesis.

Kozuki *et al.*^[165] further clarified the antioxidant activity of resveratrol in a study of AH109A liver cancer cells subjected to HX-XO treatment, finding that it significantly impaired the invasion of these HCC cells without any corresponding impact on their proliferation. These same authors also found that resveratrol could upregulate the expression of HGF in response to ROS^[166],

with these inhibitory effects being attributable to the antioxidant properties of resveratrol and metabolites thereof. In rats, oral resveratrol administration was similarly linked to detectable serum resveratrol concentrations, which enabled it to prevent the invasion of liver cancer cells. Resveratrol was able to considerably reduce AH109A cell invasion in addition to having mild inhibitory effects on HGF expression *in vivo*.

HGF signaling pathway members can activate signaling through multiple pathways, including the PI3K, Grb2, Gab1, and Src pathways, *via* specific interactions with the surface receptor protein c-MET^[167]. When these signaling pathways are activated, this can augment HCC cell invasion. HGF signaling is also associated with upregulating urokinase-type plasminogen activator (u-PA) expression in HCC cells through c-Met receptor activation^[168].

The HGF/c-Met signaling axis is essential for HCC pathogenesis^[169]. When this pathway is hyperactivated, it can contribute to both the onset and progression of HCC. Elevated c-Met expression is closely related to a poor HCC patient prognosis^[169].

Gao *et al.*^[170] revealed that resveratrol was able to inhibit Hep3B, MHCC97-L, and MHCC97-H cell invasion by downregulating HGF/c-Met pathway activity. While longer-term resveratrol administration considerably decreased membrane c-Met expression, short-term treatment significantly attenuated HGF-mediated c-Met pathway activation. Resveratrol has also been shown to slow HCC tumor growth *in vivo* significantly.

As a metastasis-related protease, u-PA protein levels and activity reductions can limit liver cancer cells' migratory and invasive activity^[171]. Yeh *et al.*^[172] found that resveratrol could downregulate this metastasis-associated protease by regulating specificity protein (SP-1), thus suppressing the metastatic progression of HCC. Specifically, resveratrol was found to limit the expression of u-PA by inhibiting SP-1 binding to its upstream promoter region. Resveratrol can also inhibit c-Jun N-terminal kinase 1/2 (JNK1/2) phosphorylation, thereby modulating the ability of SP-1 to bind the DNA. The anti-metastatic effects of resveratrol in HCC are thus related to the control of SP-1 and u-PA expression.

5.1.3 Inhibition of invasion and metastasis through VEGF-associated pathways

As a mitogenic factor, VEGF can specifically impact endothelial cell glycosylation, thereby altering vascular permeability and promoting angiogenesis^[173]. VEGF can also promote HCC cell proliferative, invasive, and metastatic growth, with its upregulation associated with worse patient outcomes^[174,175]. Negatively regulating VEGF has been demonstrated to significantly hamper liver cancer cell malignant hyperplasia while improving clinical outcomes.

Zhang *et al.*^[176] found that resveratrol could effectively inhibit HCC cell invasion by modulating hypoxia-associated HIF-1 α accumulation and VEGF expression. Based on these results, resveratrol can significantly suppress the basal and hypoxia-induced accumulation of HIF-1 α within tumor cells at the protein level without any corresponding transcriptional effects. Furthermore, resveratrol significantly reduced hypoxia-induced VEGF promoter activity, which in turn led to a decrease in VEGF expression both at the mRNA and protein levels. Mechanistically, these effects were linked to resveratrol-mediated decreases in the half-life of the HIF-1 α protein due to its increased degradation by the 26S proteasome. In addition, resveratrol substantially

decreased hypoxia-mediated ERK1/2 and Akt signaling activity, reducing the accumulation of HIF-1 α proteins and the transcriptional activation of VEGF.

NF- κ B signaling is closely associated with the induction of angiogenic activity by HepG2 cells^[177]. Yu *et al.*^[178] found that resveratrol effectively suppressed the expression of VEGF by suppressing NF- κ B activation, leading to significantly decreased mRNA and protein levels of VEGF. *In vivo*, these researchers confirmed resveratrol's ability to suppress tumor growth and vascular density in nude mice. Yu *et al.*^[179] also noted the ability of resveratrol to suppress TNF- α -induced MMP-9 activation and expression of NF- κ B, ultimately attenuating HepG2 cell invasion.

5.2 Induction of apoptosis and cell cycle regulation

5.2.1 Induction of apoptosis

In 2002, Sun *et al.*^[180] explored the ability of resveratrol to exert inhibitory effects on H22 cells and observed extensive apoptotic body formation in treated cells *via* electron microscopy. However, no corresponding mechanistic analyses were conducted.

PTEN^[181] and Bcl-xl^[182] are key proteins associated with the growth and apoptosis of cells, respectively. Resveratrol-treated HepG2 cells reportedly exhibited reductions and increases in PTEN and Bcl-xl mRNA levels^[183]. Mutating or deleting PTEN can decrease apoptotic induction and enhance proliferative activity. In contrast, Bcl-xl overexpression can inhibit apoptosis, and such changes have been linked to chemoresistance in many types of cancer.

Kuo *et al.*^[184] found that resveratrol can induce the apoptosis of HepG2 cells through a mechanism dependent on p53 while inhibiting hepatoma cell proliferation and selectively suppressing p53-positive HepG2 cell growth. Cells treated with resveratrol displayed G1 phase cell cycle arrest linked to elevated p21 expression. After resveratrol treatment, these cells likewise showed increased Bax expression, but there was no discernible change in the functioning of the Fas/APO-1 apoptotic signaling pathway. On the other hand, resveratrol administration did not significantly change p21 or Fas/APO-1 expression levels, nor did it hinder the proliferation of p53-deficient Hep3B cells.

Choi *et al.*^[185] explored the ability of resveratrol to affect the SK-HEP-1 human liver cancer cell line, ultimately determining that it inhibits the proliferation of these cells, induces ROS production, and induces DNA single-strand break formation. The authors ultimately identified Rab27 as upregulated following treatment, whereas annexin A8, thymidine kinase, maspin, peroxiredoxin-2, and guanylate-binding protein were downregulated. Resveratrol thus promotes SK-HEP-1 cell apoptosis by affecting the expression of ROS pathways and apoptotic signaling proteins.

5.2.2 Regulation of the cell cycle

Stervbo *et al.*^[186] found that resveratrol can inhibit HepG2 cell proliferation through the induction of apoptosis and the disruption of cell cycle progression. Precisely, treatment for just 2 h with resveratrol dose-dependently inhibited DNA synthesis (half maximal inhibitory concentration (IC₅₀) = 15 μ mol/L) in these cells. Treated HepG2 cells also presented with increased nuclear granularity and size during the G1 and S cell cycle phases.

Through a series of experiments performed with the transplanted H22 tumor model of HCC in mice, Yu *et al.*^[187] examined the impact of resveratrol treatment on cyclin D1,

cyclin B1, and p34cdc2. Reduced cyclin B1 and p34cdc2 protein levels were noted in tumor-bearing mice treated with resveratrol, whereas cyclin D1 levels were not significantly altered. The antitumor activity of resveratrol may thus be related to the inhibition of cell cycle progression mediated by the downregulation of particular subsets of cyclins.

Notas *et al.*^[188] determined that several mechanisms underlie the ability of resveratrol to suppress HepG2 cell proliferation. Resveratrol can initially slow progression through the cell cycle and trigger cell cycle arrest. It can additionally act as an antioxidant to limit oxidative stress within cells, thereby limiting their proliferative growth. Resveratrol can also regulate nitric oxide synthase (NOS) expression and activity, producing elevated nitric oxide (NO) levels and ultimately hamper malignant cell growth.

5.2.3 Induction of autophagy

Zhang *et al.*^[189] found that the antitumor effects of resveratrol in HCC are associated with autophagic induction. Resveratrol upregulated the autophagy-related Beclin1 and LC3 II/I proteins in a dose-dependent manner while decreasing the expression of p62, with increased Beclin1 expression perhaps mediated by p53 and the Akt pathway. Administering resveratrol led to p53 upregulation and a reduced p-Akt/Akt ratio in HCC cells. In contrast, treatment with a p53 and an Akt activator markedly reduced Beclin 1 expression, consistent with the findings observed following treatment with resveratrol.

Liao *et al.*^[190] systematically examined the impact of resveratrol on the Huh-7 human hepatoma cell line and the underlying mechanism of action. They discovered that resveratrol substantially decreased Huh-7 cell viability by inducing S-phase arrest and apoptosis. These alterations were mediated by p21WAF1 overexpression and downregulation of CDK2, cyclin A, and cyclin E, limiting cells' capacity to advance through the S phase of the cell cycle. Resveratrol also induced the autophagic death of these cells through the p38 and ERK1/2 pathways.

5.3 Preliminary summary

As discussed above, resveratrol has been shown to suppress the growth and malignancy of liver cancer cells through cell cycle arrest, apoptotic induction, and the suppression of growth factor signaling. Specifically, resveratrol can induce NOS-mediated apoptosis and cell cycle arrest in these liver cancer cells through p53-dependent mechanisms. In addition to its direct effects on HCC cells, resveratrol can affect cancer-associated cell populations. For example, it suppresses HSC-driven HCC progression by targeting HFG-C-MET signaling. It can additionally downregulate metastasis-associated proteases by regulating SP-1 to inhibit the metastatic growth of liver tumors.

Despite these promising results, ongoing research will be vital to fully clarify the mechanisms through which resveratrol affects liver cancer and the clinical settings in which it can be most effectively applied. For instance, different liver cancer-associated cell types may exhibit variable resveratrol sensitivity, ultimately shaping treatment efficacy. Future research focusing on the effective transport of resveratrol to liver cancer cells and overcoming medication resistance will be invaluable in controlling this disease. As the processes by which resveratrol acts are better understood, it may be possible to design more effective treatments and improve patient outcomes by combining this phytochemical with radiation, chemotherapy, and other treatment techniques. In summary, resveratrol has excellent promise as a future treatment for liver cancer.

6 Resveratrol inhibits CRC progression

CRC is a highly prevalent and deadly disease at the global level^[191, 192]. The complex pathogenic mechanisms that underlie colorectal carcinogenesis have been characterized in growing detail, leading to the identification of several natural compounds with promising anticancer activity against this malignancy, including resveratrol^[193]. This section provides a discussion of studies focused on the effects of resveratrol in colon cancer, focusing on the mechanisms through which it functions, the identification of promising therapeutic targets, and the evaluation of its ability to synergize with other treatment strategies, thus providing a foundation for further research exploring the effective management of colon cancer.

6.1 Inhibition of CRC cell growth and proliferation

Li *et al.*^[194] performed topological analyses that identified five critical targets of resveratrol treatment in CRC, including AKT1, IL-6, p53, VEGF, and MAPK1. Human CRC tissue samples exhibit an elevation of AKT and IL-6 protein levels, accompanied by similar changes in these proteins in the bloodstream. *In vitro* pharmacological investigations on resveratrol-treated HCT-116 cells demonstrated the compound's capacity to inhibit cell proliferation and induce apoptosis, concurrently decreasing AKT1 and IL-6 levels in the treated cells.

Gong *et al.*^[195] found that resveratrol can inhibit HTC-116 CRC cell proliferation by promoting the transcript and protein level downregulation of COX-2, which was upregulated in CRC tumor cells relative to normal colorectal cells.

6.2 Induction of CRC cell apoptosis

Qin *et al.*^[196] determined that resveratrol could inhibit HCT-116 cell proliferation by inducing cell cycle arrest and apoptotic death. These effects were attributed to Hippo/YAP pathway activation and the disruption of YAP interactions with TEAD. In molecular docking analyses, the binding of resveratrol to YAP-TEAD through van der Waals forces, π -alkyl interactions, and π - π stacking interactions was observed. Molecular analyses confirmed that resveratrol can enhance YAP phosphorylation while reducing total YAP protein levels in cells and downregulating the YAP target genes *CTGF* and *CYR61* at the mRNA level^[197].

Zhou *et al.*^[198] performed mechanistic analyses of the impact of resveratrol on CRC cells, determining that it can activate SIRT1, thereby reducing FOXQ1 expression and promoting autophagy-associated apoptotic death. They validated that resveratrol can directly activate SIRT1, preventing the expression of FOXQ1, using several complementary techniques. Furthermore, they verified that ATG16L is a crucial downstream effector protein triggered by SIRT1-mediated autophagy. The scientists used the AOM/DSS-induced colitis-associated colon cancer animal model systems and subcutaneous tumor models to validate these processes further. They emphasized resveratrol's capacity to fight CRC.

Al-Zharani *et al.*^[199] used Caco-2 cells as an *in vitro* model system and determined that resveratrol treatment led to ROS accumulation in these cells together with the upregulation of SOD, which converts ROS into H₂O₂. Furthermore, resveratrol-exposed Caco-2 cells showed significant DNA damage and upregulated p53, Bax, and caspase-3. Collectively, these findings point to resveratrol's capacity to trigger apoptosis and impede the advancement of CRC.

Fu *et al.*^[200] used HCT-116 and SW620 cells to explore the

ability of resveratrol to inhibit CRC development. In addition to dose-dependently reducing the viability of both CRC cell lines, resveratrol increased Bax, cytochrome C, cleaved caspase-9, and cleaved caspase-3 protein levels in these cells while reducing Bcl-2 protein levels. The ability of resveratrol to induce CRC cell apoptosis may thus be linked to the activation of the ROS-mediated mitochondrial signaling pathway.

Liu *et al.*^[201] additionally probed the mechanisms through which resveratrol can induce p53-mediated apoptosis in CRC cells were probed, and the stability of p53 was enhanced. *In vitro*, they confirmed that resveratrol could induce the apoptotic death of HCT-116, CO115, and SW48 CRC cells through mechanisms linked to SET7/9 upregulation. Higher SET7/9 levels led to the induction of methylated p53 at K372 and the overexpression of p53 and associated target genes. Relative to control cells, resveratrol-treated cells presented with significant increases in p53 upregulated modulator of apoptosis (PUMA) and Bax expression. In the absence of SET7/9, resveratrol exhibited significantly reduced efficacy.

Li *et al.*^[202] found that resveratrol can induce apoptotic death and G1 phase arrest of tumor cells through selective targeting of the AKT signaling axis. *In vitro*, they demonstrated that resveratrol inhibited dihydrolipoamide dehydrogenase 1 (DLD1) and HCT15 cell proliferation and colony formation without any corresponding effect on normal colon epithelial cells. Molecular docking and *in vitro* pull-down tests have shown that resveratrol can directly bind to AKT1 and AKT2. Resveratrol therapy decreased the amounts of apoptosis-regulating proteins cyclin D1, cyclin E2, and Bcl-2 in cells while concurrently upregulating Bcl-2-associated X proteins and p53. Comparable effects have been documented with the knockdown of AKT1/2.

Zhang *et al.*^[203] found that resveratrol can inhibit CRC progression by targeting the AMPK/PGC-1 α signaling pathway, an essential regulator of proliferative activity, differentiation, migration, and programmed cell death. CRC cells presented with reduced AMPK and PGC-1 α expression, whereas these factors were upregulated upon resveratrol treatment. In parallel with these changes, the authors noted that resveratrol enhanced Fas, FasL, and Bax expression while suppressing the expression of Bcl-2.

The Sonic hedgehog (Shh) ligand is a crucial driver of Hh signaling pathway activity, and Du *et al.*^[204] uncovered the ability of Shh to protect HCT-116 cells from undergoing apoptotic death, leading to enhanced tumor cell viability. Shh can promote the upregulation of Ptch, Smo, and Gli-1. Still, resveratrol can inhibit such Shh-mediated Ptch, Smo, and Gli-1 upregulation, ultimately inducing apoptotic death that protects against CRC progression.

6.3 Inhibition of CRC cell invasion and metastasis

NF- κ B is a crucial regulator of factors, including cyclin-related proteins, angiogenic factors, inflammatory cytokines, and components of key survival and growth-related pathways involved in tumor development^[205]. The inhibition of NF- κ B has been established as a key approach to treating CRC. Dariya *et al.*^[206] employed molecular docking and molecular dynamics simulation strategies to demonstrate hydrogen bond formation between resveratrol and NF- κ B, with a binding energy of -5.58 kcal/mol. The authors further confirmed that resveratrol can induce the accumulation of NF- κ B within the cytosol while limiting its ability to translocate to the nucleus.

Gao *et al.*^[207] found that resveratrol can inhibit CRC metastasis through the miR-125b-5p/TRAF6 signaling pathway. They found that miR-125b-5p overexpression can specifically inhibit HCT-8

cell migration and invasion because it targets TNF receptor associated factor 6 (TRAF6), which can activate AKT/GSK-3 β /SNAIL signaling to promote CRC metastasis. Resveratrol can limit TRAF6-associated signaling, suppressing migratory and invasive development *via* stabilizing miR-125b-5p in CRC cells. The inhibitory effects of resveratrol on CRC metastasis might be reversed by either overexpressing TRAF6 or downregulating miR-125b-5p.

Buhrmann *et al.*^[208] demonstrated the ability of resveratrol to reduce the activity of HCT-116 and SW480 CRC cells. SIRT1 overexpression, FAK downregulation, and decreased focal adhesion formation were linked to the underlying mechanism of action. Furthermore, these researchers discovered that resveratrol could prevent NF- κ B activation and the ensuing overexpression of NF- κ B target genes related to invasion, survival, and metastatic progression.

TNF superfamily members play significant roles in tumor development, progression, invasive growth, and metastasis. In addition to enhancing its secretion, TNF can stimulate the upregulation of a wide range of other inflammatory cytokines and chemokines. An early study in 1985 revealed that macrophages and T cells can produce TNF- α and TNF- β , triggering tumor development and NF- κ B activation through its pro-inflammatory effects.

Buhrmann *et al.*^[209] found that through TNF- β downregulation and a reduction in the phosphorylation and nuclear translocation of p65, resveratrol is capable of suppressing CRC cell proliferative, invasive, and enhancing apoptotic activity. Furthermore, it was shown to prevent TNF- β -induced I κ B kinase (IKK) activation and I κ B α phosphorylation, which in turn prevented the NF- κ B pathway from being activated. In addition, resveratrol caused caspase-3 to be upregulated and MMP-9, cyclin D1, Ki-67, and CXCR4 to be dose-dependently downregulated. These results point to resveratrol's capacity to suppress TNF- β /NF- κ B signaling and produce its anticancer effects.

This same team further examined the effects of TNF- β on EMT induction in RKO, HCT-116, and SW480 cells.^[210] While TNF- β was found to induce the morphological and protein level changes associated with the acquisition of a mesenchymal-like phenotype, resveratrol significantly reversed these changes, thus arresting EMT induction.

Dermani *et al.*^[211] found that resveratrol could inhibit HCT-116 cell invasion, proliferation, and EMT induction *via* the upregulation of miR-200c. These researchers found that downregulating E-cadherin and increasing vimentin and zinc finger E-box binding homeobox 1 (ZEB-1) expression occurred when they experimentally decreased miR-200c expression. Under these circumstances, HCT-116 cell migration was also increased, and the apoptosis rate was significantly reduced. Treatment with resveratrol reversed these alterations and restored miR-200c expression, resulting in a transformation from an EMT phenotype to a MET phenotype.

Lee *et al.*^[212] additionally explored the ability of resveratrol to inhibit HCT-116 and SNU81 cell invasion, proliferation, and metastasis. In addition to upregulating TTP through the downregulation of E2F transcription factor 1 (E2F1) to hamper CRC cell growth and metastasis, they ultimately determined that resveratrol was able to enhance TTP inhibitory activity in these cells by negatively regulating the expression of cellular inhibitor of apoptosis proteins 2 (cIAP2), E2F1, large tumor suppressor kinase 2 (LATS2), and lin-28 homolog A (Lin28).

Yuan *et al.*^[213] found resveratrol can reverse the EMT status of

CRC cells while inhibiting their invasive and migratory activity by controlling the AKT/GSK-3 β /Snail pathway. In particular, the scientists discovered that AKT1 silencing and resveratrol therapy inhibited the migration and invasion of SW480 and SW620 cells, enhanced the expression of E-cadherin, and decreased the levels of N-cadherin, p-AKT1, p-GSK-3 β , and Snail in these tumor cells. The underlying mechanisms were confirmed *in vivo*, significantly inhibiting CRC metastasis in the lung.

Raf-1 kinase suppressor protein (RKIP) is a Raf-1, PI3K, and MAPK inhibitor that can suppress the metastasis of CRC^[214]. Dariya *et al.*^[215] determined that resveratrol can induce the protein level expression of RKIP to inhibit CRC metastasis effectively. They also detected strong binding between resveratrol and RKIP in molecular docking analyses.

6.4 Preliminary summary

As previously mentioned, numerous investigations have demonstrated how resveratrol can impact CRC cells. These mechanisms include the suppression of CRC cell migration and invasion, the activation of the AKT/GSK-3 β /Snail pathway, and reversing EMT induction. Additionally, resveratrol can inhibit COX-2 expression and restrict CRC cell invasion and proliferation via interacting with RKIP. Resveratrol can modify the TME in addition to its direct cytotoxic effects, as research has shown that it changes the function of the ATP-binding cassette (ABC) transporter, which modifies drug sensitivity and transport.

Several crucial topics might require additional exploration. For instance, a more thorough characterization of the mechanisms by which resveratrol influences CRC is necessary, especially concerning their interactions with specific signaling pathways. Strategies for enhancing resveratrol's bioavailability and selectivity must also be developed to reduce off-target effects and increase therapeutic efficacy. Studies of the synergistic potential of combining resveratrol and chemotherapy, radiotherapy, or other treatments may also help achieve better treatment outcomes. Finally, further clinical trials will be crucial to comprehensively evaluate resveratrol's safety and efficacy in managing CRC. Resveratrol demonstrates considerable potential as a therapeutic agent for CRC management, and further clarification of its mechanisms, along with corroborative clinical research, may offer affected patients the prospect of improved treatment outcomes.

7 Clinical trials of resveratrol against gastrointestinal tumors

To date, a substantial body of clinical trials has rigorously examined the therapeutic effects of resveratrol. Furthermore, multiple Phase III and IV clinical trials assess its viability as a pharmaceutical agent and food additive. The treatment conditions under investigation include metabolic and cardiovascular disorders, cancer, central nervous system diseases, inflammation, aging, and others^[216].

A simple search of the PubMed database in October 2024 produced nearly 4,900 results for the query "resveratrol and cancer." Refining the search to encompass only clinical trials yielded a scant 31 relevant studies, most of which predominantly investigated the general pharmacokinetics of resveratrol. The absence of clinical trials highlights that resveratrol affects various cellular pathways, with its effectiveness contingent upon multiple factors, including cancer kind and stage, dosage, and therapy length. Of the results of this search, three studies focused on gastrointestinal tumors.

Patel *et al.*^[217] investigated the concentration of resveratrol and its metabolites in human colorectal tissue following resveratrol ingestion. Their study demonstrated that daily doses of 0.5 and 1.0 g of resveratrol can attain pharmacologically effective concentrations within the human gastrointestinal tract.

The safety, pharmacokinetics, and pharmacodynamics of micronized resveratrol (SRT501) were assessed in research by Howells *et al.*^[218]. Patients scheduled for hepatectomy who had colon cancer and liver metastases made up the study population. For 14 days, these patients were given 5.0 g of SRT501 every day. The mean plasma concentration of resveratrol following a single dose of SRT501 was measured at $(1,942 \pm 1,422)$ ng/mL, representing a 3.6-fold increase compared to the reported levels for the equivalent dosage of non-micronized resveratrol. Furthermore, the administration of SRT501 resulted in the detection of resveratrol concentrations reaching up to 2,287 ng/g in liver tissue samples. Surprisingly, after receiving SRT501 medication, the levels of lytic caspase-3 in malignant liver tissue increased by 39% compared to tissue samples from patients who received a placebo. These results imply that more clinical research is necessary to evaluate the possible therapeutic advantages of SRT501.

Ostwal *et al.*^[219] undertook a single-arm Phase II clinical trial to evaluate the efficacy of an oral pro-oxidant combination of resveratrol and copper (R-Cu) in mitigating toxicity among patients with advanced GC receiving docetaxel-based multidrug chemotherapy. The study found that R-Cu effectively reduced the incidence of non-hematological toxicity, thereby facilitating the maintenance of dose intensity and potentially improving treatment outcomes. R-Cu was associated with a reduction in docetaxel exposure relative to the control group while maintaining comparable overall survival efficacy.

Recent clinical studies on the anti-tumor effects of resveratrol have produced encouraging results. Current research emphasizes its potential with traditional therapy, novel drug delivery technologies, and its effectiveness across diverse cancer types. Ongoing study is crucial for thoroughly comprehending the processes by which resveratrol operates and augmenting its therapeutic efficacy in oncology.

8 Summary and outlook

Gastrointestinal tumors represent a severe threat to the health of individuals throughout the world. First-line drugs currently used for the clinical management of these tumors are associated with drawbacks, including inadequate efficacy and a high potential for disruptive side effects. Reduced toxicity and adverse consequences. Therefore, there is an urgent need for treatments for such cancers. Resveratrol demonstrates food-medicine similarity, moderate toxicity and adverse effects, and significant anticancer efficacy. As highlighted in this review, resveratrol has been shown to counteract the growth of several cancer types, including esophageal, gastric, liver, pancreatic, and CRCs, through myriad mechanisms. These underlying mechanisms include the suppression of growth, proliferation, invasion, and metastasis, the disruption of normal cell cycle progression, and the induction of autophagy and apoptosis. *In vitro* and *in vivo* research has confirmed the efficacy of resveratrol for managing gastrointestinal tumors, providing a solid foundation for applying food-medicine homology in the clinic.

Further study is essential in this area despite increased interest in using resveratrol in treating tumors. Predicting results in the

clinic is still difficult because, despite resveratrol's encouraging *in vitro* performance, there have not been many equivalent *in vivo* studies. In light of biotechnological advances, efforts to employ a range of additional advanced techniques to more fully document the antitumor effects of resveratrol and the underlying mechanisms are warranted. Employing novel model systems, such as patient-derived organoids, explants, and xenografts, can substantiate the efficacy of resveratrol treatment, enhancing the therapeutic relevance of these research endeavors. Moreover, personalized medicine strategies, including identifying genetic biomarkers that forecast responsiveness to resveratrol, may facilitate the customization of its application for individuals most likely to benefit from this therapy.

Data availability

Not applicable.

Conflicts of interest

The authors declare that there are no conflicts of interest in work. Mengyao Li is an Editorial Board Member of Food & Medicine Homology, but was not involved in the processing, peer review or decision making of this article.

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Author contribution statement

Meng-Yao Li: project administration, manuscript writing, manuscript revision, figure preparation. **Ao Gu:** manuscript revision. **Jia-Tong Li:** manuscript revision. **Nan-Nan Tang:** manuscript revision. **Maima Matin:** manuscript revision. **Ge Zhang:** project administration, manuscript revision. **Atanas G Atanasov:** project administration, manuscript revision. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

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