Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Dietary pterostilbene and cancer: a critical review on its molecular mechanisms and therapeutic potential

Nidesha Randeni[a], Yilin Wang[b], Shujia Zhou[b], Baojun Xu[a,*]

[a] Food Science and Technology Program, Department of Life Sciences, Beijing Normal-Hong Kong Baptist University, Zhuhai 519087, China
[b] Beri Pharma Co., Ltd., Zhuhai 519090, China

ARTICLE INFO

Article history:
Received 10 October 2024
Received in revised form 26 November 2024
Accepted 12 March 2025

Keywords:
Stilbene
Tumor
Chemoprevention
Signaling pathways
Natural products
Blueberry

ABSTRACT

Cancer remains a significant global health challenge, necessitating the exploration of novel therapeutic strategies. Natural compounds have emerged as promising candidates for cancer treatment due to their diverse pharmacological activities and relatively low toxicity. Among these, pterostilbene, a natural stilbenoid found mostly in blueberries and grapes, has garnered increasing attention for its potential anti-cancer properties. Pterostilbene has been shown to modulate multiple molecular mechanisms involved in cell proliferation, apoptosis, autophagy, angiogenesis, and metastasis by targeting multiple signaling pathways, including PI3K/Akt/mTOR, AMPK, MAPK/ERK, JAK/STAT, and NF-κB. Evidence from studies on various cancer types highlights its capability to suppress tumor growth, modulate oxidative stress, and inhibit inflammation. Furthermore, preclinical studies have demonstrated the ability of pterostilbene to inhibit tumor growth, induce apoptosis, and enhance the efficacy of conventional chemotherapy drugs. Overall, pterostilbene holds promise as a novel therapeutic agent for cancer treatment, offering potential benefits for improving patient outcomes and quality of life. So, this review provides a comprehensive overview of the molecular mechanisms underlying pterostilbene's anti-cancer effects and evaluates its role as a potential therapeutic agent in cancer treatment.

1. Introduction

Today, cancer remains one of the main worldwide challenges, as the new GLOBOCAN 2022 data indicate that more than 20 million new cancer cases and more than 10 million cancer mortalities are registered worldwide in 2022. The most common cause of cancer-related mortality is still lung cancer. Other prevalent malignancies include breast, colon/rectum, prostate, and stomach cancer. Such numbers speak volumes about the severity of the call for effective and novel approaches toward impending this disease[1].

The establishment of chemotherapy, radiotherapy, surgery, and immunotherapy has greatly enhanced the life quality and survival rates of several cancer patients. Nevertheless, these proposed approaches have significant drawbacks. Radiotherapy and chemotherapy have many side effects, for instance, nausea, fatigue, immune suppression, and organ damage due to their non-targeted nature, and are toxic to both healthy cells and cancerous cells[2]. Furthermore, chemotherapy resistance, either primary or secondary, remains a significant issue for long-term cancer management[3]. In the same manner, immunotherapy is another efficient method with some drawbacks; it has immune-related side effects, high costs, and effectiveness is different among patients[4]. The lack of specificity and relatively high toxicity of these compounds present a strong rationale for the development of novel or adjunct treatments with a superior safety profile and outcome.

* Corresponding author at: Food Science and Technology Program, Department of Life Sciences, Beijing Normal-Hong Kong Baptist University, Zhuhai 519087, China
E-mail address: baojunxu@bnbu.edu.cn (B.J. Xu).
Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2025.9250592

In this context, the dire need for innovative therapeutic approaches in cancer therapy and prevention is highlighted by the disease's dismal prognosis and decreased overall survival rate. This has motivated us to develop novel cancer treatment compounds that are particularly derived from natural materials and have minimal side effects. The biological benefits of naturally occurring polyphenols, specifically stilbenes, which are found in food and plants, have made them more significant in the prevention of cancer. These features include anti-inflammatory, antioxidative, antiproliferative, and proapoptotic actions[5].

Among these natural compounds, pterostilbene (3,5-dimethoxy-4′-hydroxystilbene), a dimethylated derivative of resveratrol (3,5,4′-trihydroxystilbene) found abundantly in blueberries, grapes, and other plants, has emerged as a subject of intense investigation for its potential anti-cancer effects[6]. Pterostilbene, as a polyphenol, has garnered increased attention as a possible anticarcinogen with no toxic or detrimental side effects[7]. While resveratrol and pterostilbene share similar pharmacological properties, such as hypolipidemic activity, anti-diabetes, anticancer, and beneficial effects on the central nervous system and cardiovascular diseases, pterostilbene exhibits stronger antioxidant and anticancer effects[8].

Pterostilbene has been shown to have anti-cancer effects in a variety of *in vitro* and *in vivo* settings, including the ability to suppress angiogenesis, prevent metastasis, induce apoptosis, and inhibit proliferation in many cancer types by regulation of signaling pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK). Since pterostilbene can govern these pathways and due to the change in the anti-inflammatory, antioxidant, and pro-apoptotic features, further research is merited.

The goal of this review is to give a general understanding of the current literature on the molecular level of pterostilbene for its anticancer properties, with particular emphasis on its impacts on signaling pathways. To this end, we hope to discover the comparative degree of its therapeutic efficacy and the following critical issues that need to be resolved for its application in clinical settings. The ideas laid here will inform subsequent research and foster the pursuit of novel pterostilbene application in cancer therapy.

2. Pterostilbene: an overview

Pterostilbene, also known as 3,5-dimethoxy-4'-hydroxystilbene, is a naturally occurring substance that falls within the class of stilbene derivatives under the polyphenolic compounds class. It is produced by plants using the phenylpropanoid and/or polyketide pathway and has a phenolic unit and no nitrogen-based functional groups in its structure group[9]. Many plant species, including those that humans eat or utilize as traditional medicinal herbs, may synthesize stilbenes[10]. For instance, the traditional Chinese medication radix *Polygoni multiflora* (*Fallopia multiflora*) has been shown to contain a variety of stilbene compounds, such as polydatin, resveratrol, 2,3,5,4-tetrahydroxystilbene-2-*O*-*β*-*D*-glucoside, and pterostilbene[11]. The first known isolation of pterostilbene, a secondary metabolite generated by plants, came from the heartwood of *Pterocarpus santalinus*, better known as red sandalwood[12].

Furthermore, because pterostilbene absorbs more quickly and may be disseminated throughout the body, it has been demonstrated experimentally to have more acceptable metabolic stability and better oral bioavailability[13]. Recent findings from toxicity studies using human and animal models showed that pterostilbene is generally safe to eat and does not have any serious side effects or toxicity[14]. The hematocrit count and red blood cell count increased in mice when pterostilbene was fed to them[15]. Additionally, the oral ingestion of pterostilbene did not result in toxicity-related changes or abnormalities, according to histological investigations of the liver, spleen, kidneys, heart, brain, lungs, and pancreas[12]. Furthermore, a clinical investigation demonstrated that pterostilbene is safe to ingest in proportions that protect hPDLSCs from damage generated by TNF-α by lowering pro-inflammatory mediator levels of interleukin-6 (IL-6) and IL-1β and inhibiting NF-κB (p65) activation[16].

2.1 Chemical structure and properties

The 2 most well-known and extensively researched stilbenes are pterostilbene and resveratrol. They both contain a C6-C2-C6 and 2 phenyl rings joined by an ethene double bond, which is nearly identical to the chemical structure of other stilbenes[6]. The production of pterostilbene from resveratrol can occur both *in vitro* and in planta in grapevine (*Vitis vinifera*) leaves under stressors such as UV radiation exposure and fungus infection (*Plasmora viticola*)[12]. The shikimate route, which uses the amino acids phenylalanine or tyrosine, can be used to biosynthesize pterostilbene. These 2 amino acids are transformed into *p*-coumarate and subsequently *p*-coumaroyl-CoA, a stilbene precursor, *via* the shikimate pathway. Resveratrol is produced by the catalytic conversion of *p*-coumaroyl-CoA by stilbene synthase. Finally, resveratrol is transformed into pterostilbene by *O*-methyltransferase, which does this by methylating 2 of resveratrol's hydroxyl groups[17]. That being said, the distinction in the presence of methoxy as well as hydroxyl groups connected to their phenyl rings gives pterostilbene superior pharmacokinetic qualities over resveratrol[18]. When compared to resveratrol without methoxy groups but with three hydroxyl groups on the phenyl ring, the higher lipophilicity caused by the presence of 2 methoxy groups on the A phenyl ring and 1 hydroxyl group on another benzene ring was reported to be the cause of the increased cellular uptake[19]. The differences in pterostilbene and resveratrol's chemical structures are illustrated in Fig. 1.

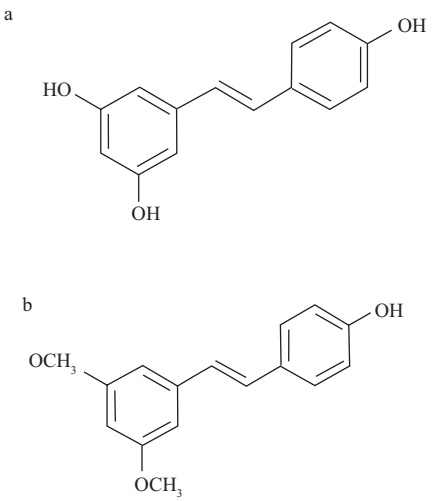

Fig. 1 Chemical structures of (a) resveratrol and (b) pterostilbene.

2.2 Sources of pterostilbene

2.2.1 Natural sources

It has been shown that a variety of plant materials used in human diets may produce pterostilbene to various extents (Table 1). *P. santalinus*, also known as red sandalwood or heartwood, was the first source of pterostilbene to be identified[8]. Notably, only a small number of plant species synthesize stilbenes, in contrast to flavonoids, which are generated by many plants. Pterostilbene has been observed to be present in comparatively smaller amounts in the leaves of grape (*V. vinifera*) and blueberry fruits, but abundantly in Indian Kino (*Pterocarpus marsupium*), *Guibourtia tessmannii*, and *Vaccinium* spp. Berries[18]. Furthermore, it has been determined that peanuts (*Arachis hypogaea*) are a source of pterostilbene[20] (Table 1). It should be mentioned, nevertheless, that many of these food sources may not contain enough pterostilbene to have been shown to have any positive effects on health. Supplements containing the pure components that have been developed provide a way to supply enough levels of nourishment. Furthermore, given the increasing interest in pterostilbene as a potentially beneficial nutraceutical ingredient, more studies are necessary to determine the chemical's presence in processed and fresh food items using standardized extraction and analytical techniques.

Table 1
Sources of pterostilbene.

Source	Concentration range	References
Blueberries	9.9–15.1 mg/kg fresh weight	[17]
Blueberries	15 μg/100 g weight	[17]
Fresh grape berries	120–530 ng/g dry sample	[21]
Vaccinium berries	99–520 ng/g dry sample	[17]
Deerberries	520 ng/g dry sample	[8]
Fungal infected grapes	0.2–4.7 mg/g fresh weight	[2]
Rabbit-eye blueberry	99–151 ng/g dry sample	[8]
Peanut	NA	[20]

Note: NA, not applicable.

2.2.2 Synthetic production

Pterostilbene can be produced through a number of methods, such as microbial fermentation and chemical synthesis. The chemical methods include the heck coupling reaction, oxidative coupling reaction, and Wittig reaction. In order to create the stilbene backbone and add the methoxy groups, the chemical synthesis of pterostilbene usually starts with a condensation reaction between suitable starting materials. In one instance, benzaldehyde and 3,5-dimethoxybenzaldehyde underwent the Wittig reaction to produce pterostilbene, which was then obtained by demethylation. This process provides an easy way to obtain high-yield and pure pterostilbene[16].

Using microorganisms that can biosynthesize pterostilbene, microbial fermentation offers an alternate method of producing this chemical. One such microbe is a strain of the fungus *Aspergillus* spp. that has undergone metabolic engineering techniques to increase its production of pterostilbene. In microbial fermentation, the designed microorganism metabolizes precursor chemicals like phenylalanine or cinnamic acid *via* enzymatic pathways to create pterostilbene. Using the metabolic powers of microorganisms, this process provides a sustainable and eco-friendly way to produce pterostilbene[22].

2.3 Health effects of pterostilbene

Pterostilbene's benefits for human health have been the subject of much research and have grown in popularity in the medical community. According to recent studies, pterostilbene has strong antioxidant, anti-inflammatory, and anticancer effects, so it is worthy of development to be used in treatment. For instance, pterostilbene was found to guard against mycotoxins that caused harm in the JAK/STAT signaling pathway *via* suppression of oxidative stress in Swine alveolar macrophage[23]. Additionally, it has also been observed that pterostilbene, through its antioxidant activity and activation of sirtuin-1 (SRT1) to prevent cardiomyocyte cell death, exhibits a cardioprotective effect against endoplasmic reticulum (ER)-induced heart damage[24]. These impacts on inflammation and cellular protection are useful precisely in utilizing the combating system against cancer since inflammation and oxidative stress are determinants in tumor growth. Moreover, pterostilbene, through the suppression of pro-inflammatory cytokine production and NF-κB, offers a reasonable therapeutic implication in cancer-contributing inflammation. Furthermore, pterostilbene affects stem cell behavior, for instance, human periodontal ligament stem cells (hPDLSCs) on their proliferation and differentiation, and subsequently downregulates TNF-α-induced inflammation[25]. Apart from being an antioxidant and anti-inflammatory compound, studies have demonstrated that pterostilbene possesses modulatory effects on some of the signaling pathways responsible for cell survival, apoptosis, and regulation of cell cycle pathways. It is evident in the above analysis that our elected compound affects pathological characteristics associated with cancer, including oxidative stress, inflammation, and cell death.

One of the key advantages of pterostilbene over conventional chemotherapy drugs is its remarkably low toxicity and minimal adverse effects. Studies have shown that pterostilbene does not exhibit significant cytotoxicity toward normal cells at therapeutic concentrations, making it a promising candidate for long-term use and combination therapies. In preclinical studies, no discernible hazardous side effects were found in animal subjects, even at a high dosage of 3 000 mg/kg·day[26]. Additionally, recent human experiments aimed at assessing pterostilbene's safety have also produced encouraging findings. These studies imply that pterostilbene is safe for ingestion by humans when given at therapeutic dosages. This is especially significant because it suggests that pterostilbene may be given to patients without producing serious adverse effects that would outweigh its advantages[27]. There are, however, insufficient long-term safety data, and some research has expressed worries about possible liver toxicity at high dosages[28]. However, higher concentrations may require further investigation to establish a definitive safety threshold for therapeutic applications.

3. Key molecular mechanisms of pterostilbene in cancer

According to Jin et al.[29] cancer is a complicated disease that is brought on by a combination of environmental and genetic variables.

These causes include genetic alterations, persistent inflammation, certain lifestyle choices, including food and smoking, and exposure to chemicals and radiation. Fundamentally, the illness is frequently caused by genetic alterations, which can be inherited or acquired throughout the course of a person's life. These mutations cause the regular cell cycle to be disrupted, which results in the uncontrolled proliferation of cells and the creation of tumors[30]. Another important element is chronic inflammation, which can lead to malignant growth and is also a source of it. This vicious cycle makes the condition worse.

Collectively, these components contribute to the multifaceted of cancer, making it difficult to comprehend and manage[31]. The mainstays of current treatment include immunotherapy, radiation, chemotherapy, and surgery; however, each has drawbacks like as medication resistance and adverse effects[32]. Traditional chemotherapy drugs are useful in oncology, but they can be expensive and have a lot of side effects. Pterostilbene stands out as a shining example because it is less expensive and has fewer adverse effects. In contrast to resveratrol, pterostilbene has higher bioactivity. Pterostilbene's potency is demonstrated by its remarkable IC_{50} value of 32.67 μmol/L, which is significantly higher than resveratrol's 108.7 μmol/L in terms of inhibitory effect on the HeLa cervical cancer cell line[33]. These qualities have not gone unnoticed, drawing the attention of an expanding community of academics who are keen to explore their possibilities further. Pterostilbene has been shown in empirical research to possess remarkable anticancer capabilities, as evidenced by its efficiency against a variety of malignant neoplasms[34]. Examining pterostilbene's mode of action reveals that its anticancer mechanisms are complex, acting on several cellular and molecular levels. Pterostilbene prevents the migration and invasion of cancer cells, 2 essential processes in the spread of cancer. According to Li et al.[35] pterostilbene may control particular enzymes linked to aging and lifespan, which may affect its anticancer qualities. Altogether, pterostilbene has been shown in multiple studies to be involved in the regulation of the epigenetic network and to have the ability to control the cancer cells' cell cycle, survival, growth, oxidative stress, autophagy, apoptosis, stemness, and additional potential for metastasis (Fig. 2).

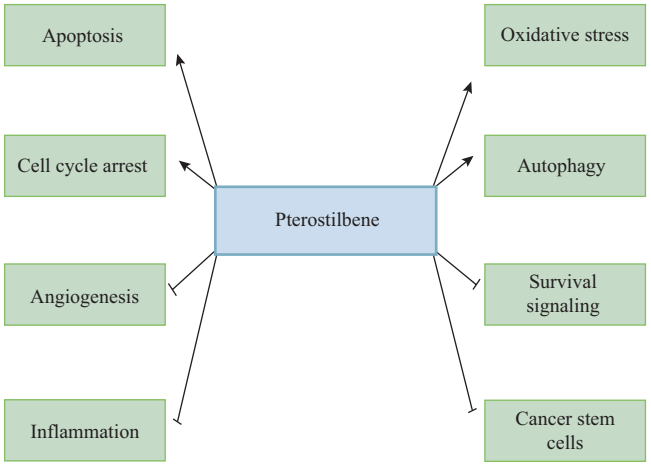

Fig. 2 Anticancer mechanism of pterostilbene.

3.1 Role of pterostilbene in modulating key cancer signaling pathways

The deregulation of several signaling pathways involved in cell proliferation, survival, and differentiation is a hallmark of cancer. These pathways, which are frequently linked together and cross-regulated, are essential for the development, spread, and metastasis of cancer. Several important signaling pathways have been linked to cancer, including MAPK/ERK, PI3K/Akt/mTOR, Wnt/*β*-catenin, Notch, Hedgehog, and transforming growth factor-beta (TGF-β) pathways[36].

In response to external cues, the MAPK/ERK pathway controls the growth, differentiation, and survival of cells. Mutations in downstream effectors or upstream receptors can cause this pathway to become dysregulated, which is a common occurrence in a variety of malignancies. Another important signaling cascade that is typically dysregulated in cancer is the PI3K/Akt/mTOR pathway, which promotes cell growth, metabolism, and survival. Tumor suppressor phosphatase PTEN depletion or mutations in the *PI3K* or *Akt* genes frequently activate this pathway[37].

Tissue homeostasis, stem cell maintenance, and cell fate determination are all significantly influenced by the Wnt/*β*-catenin pathway. Wnt signaling dysregulation plays a role in the development of cancer, especially in solid tumors like colorectal cancer. Notch signaling controls differentiation and cell fate decisions; it is typically dysregulated in solid tumors and leukemia. Among other things, medulloblastoma and basal cell cancer are linked to dysregulated Hedgehog signaling[38].

In the early stages of cancer, the TGF-β pathway functions as a tumor suppressor; however, in later stages, it promotes tumor development and metastasis. Many malignancies, including pancreatic and breast cancer, have dysregulated TGF-β signaling. The intricacy of cancer biology and treatment resistance is largely attributed to the significant interaction and cross-talk between these signaling pathways[39].

3.2 Pterostilbene's effect on cancer cell apoptosis

A well-known mechanism of programmed cell death, apoptosis, is regarded as both an essential therapeutic target and a natural barrier during the development of tumors[40]. This tightly regulated process proceeds through 2 principal pathways: the intrinsic pathway and the extrinsic pathway, also known as the mitochondrial and death receptor pathways, respectively. Cancer is characterized by dysregulation of apoptosis, which enables cancerous cells to avoid death and multiply unchecked. As a result, apoptosis targeting has become a crucial therapeutic approach in the treatment of cancer.

Many cancer cells, including those found in the bladder[41], lung[42], breast[42], colon[43], stomach, pancreatic[42], esophageal[44], cervical[45], melanoma[46], multiple myeloma[47], and lymphoma[48], may undergo apoptosis in response to pterostilbene treatment. Apoptosis is ultimately regulated by the p53 upregulated modulator of apoptosis (PUMA) or Bcl-2 protein families. The Bcl-2 protein family, which has both pro- and anti-apoptotic members, regulates the mitochondrial pathway. Pterostilbene has been shown to be able to: 1) downregulate the anti-apoptotic factors Bcl-2, Bcl-xl, and Mcl-1; 2) increase the expression of the pro-apoptotic factors Bax, Bad, Bak, and Bid; and 3) lower the mitochondrial membrane potential. Then, caspase

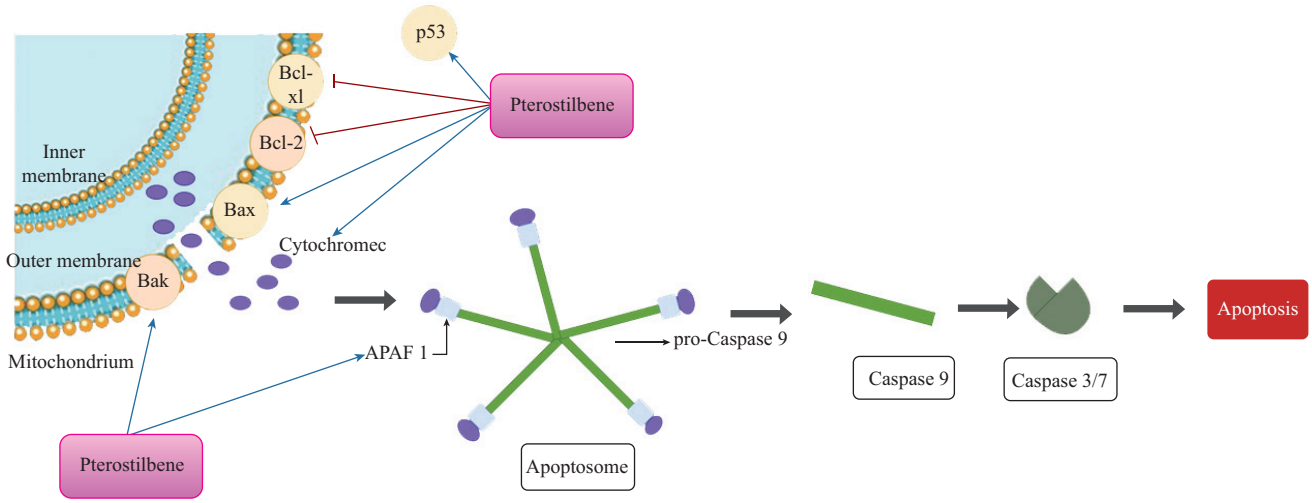

Fig. 3 Anti-cancer effect of pterostilbene on intrinsic pathways of apoptosis.

activation (Caspases-9 and -3/7) is directly induced by cytochrome c, Smac/DIABLO, and cytosol expression, which leads to programmed cell death through intrinsic and extrinsic pathways[49].

3.2.1 *Intrinsic (mitochondrial) pathway*

The intrinsic pathway of apoptosis is initiated by mitochondrial dysfunction, often triggered by cellular stress or DNA damage. The equilibrium between anti-apoptotic proteins (such as Bcl-2 and Bcl-xl) and pro-apoptotic proteins (such as Bak and Bax) controls this mechanism. When this balance shifts towards pro-apoptotic signals, mitochondrial outer membrane permeabilization (MOMP) occurs, releasing cytochrome c into the cytosol. Apaf-1, pro-Caspase-9, and cytochrome c combine to create the apoptosome complex, which activates Caspase-9 and, subsequently, Caspase-3, the executioner caspase. This cascade leads to the cleavage of cellular components and, ultimately, cell death[50]. As presented in Fig. 3, the application of pterostilbene was found to dramatically downregulate Bcl-2[51], Bcl-xl, and Mcl-1, and to significantly increase the expression of Bax, Bak, Bad, and Bid[48,51]. It was also found to lower mitochondrial membrane potential[48]. Following that, there was an increase in the release of cytochrome c and the second mitochondrial-derived activator of caspase (Smac/DIABLO) into the cytosol from the intermembrane mitochondrial space. Smac/DIABLO and cytochrome c activated Caspase-9 and Caspase-3, which resulted in apoptosis when they were released into the cytosol[48].

3.2.2 *The extrinsic (death receptor) pathway*

The extrinsic pathway, on the other hand, is activated *via* death ligand binding, such as FasL or TNF-α, to their corresponding death receptors on the cell surface. Factor-related suicide (Fas) death receptor initiates the extrinsic pathway, which in turn activates downstream caspases and finally causes apoptosis[52]. This interaction triggers the recruitment and activation of pro-Caspase-8 by the death-inducing signaling complex (DISC). Activated Caspase-8 can directly activate Caspase-3 or amplify the apoptotic signal through the intrinsic pathway by cleaving Bid, a pro-apoptotic Bcl-2 family member, to tBid, which promotes MOMP. In human T lymphoma HUT78 cells, human AGS gastric cancer cells, and mice treated with azoxymethane, pterostilbene enhanced the expression of Fas and FasL[8]. Additionally, pterostilbene has been shown to upregulate the expression of both Fas and Fas ligands. Furthermore, TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) can bind to 4 distinct receptors: DcR1 and DcR2, which are 2 antiapoptotic decoy receptors (DcRs), and DR4 and DR5, which are pro-apoptotic death receptors (DRs). Studies have indicated that pterostilbene triggers exogenous apoptosis in cancer cells, which in turn activates Caspase-3/7/8.7[53] by upregulating DR4/5 and downregulating DcR-1/2 expression. These effects of pterostilbene on extrinsic pathways are shown in Fig. 4.

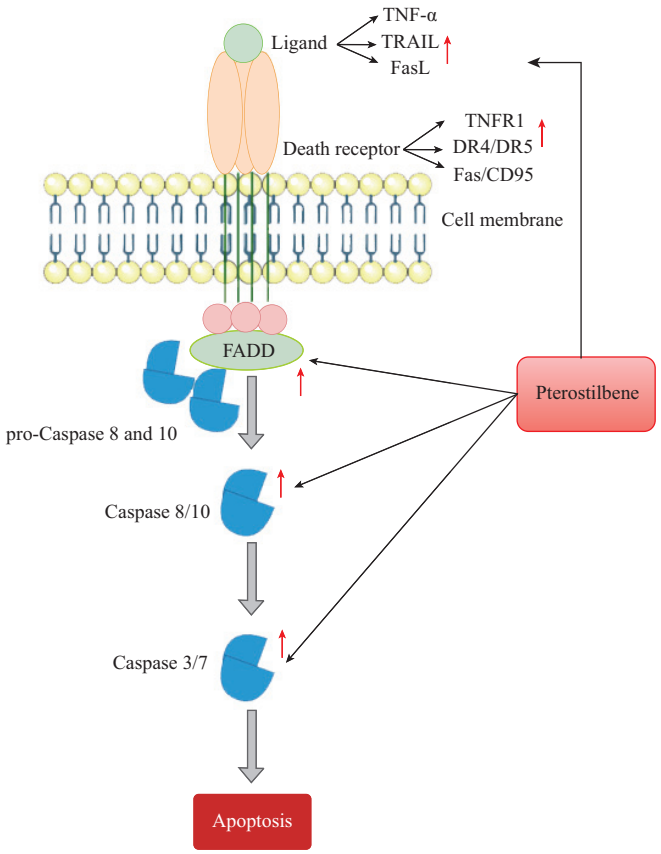

Fig. 4 Anti-cancer effect of pterostilbene on extrinsic pathways of apoptosis.

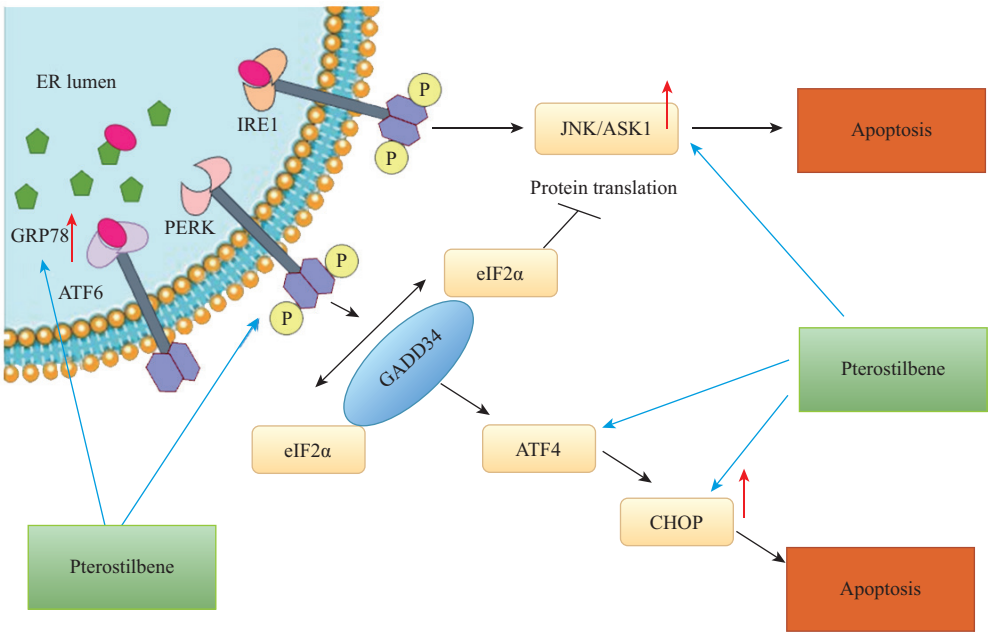

Fig. 5 Anti-cancer effect of pterostilbene on ERS pathways of apoptosis.

3.2.3 *ER stress pathway*

For the folding and modification of proteins, the storage of Ca^{2+}, and the synthesis of lipids, the ER is an essential cytosolic compartment[54]. Hypoxia and nutritional restriction are common challenges for tumors, as they disrupt the ER and cause ER stress (ERS)[55]. Persistent ERS, however, has the power to tip the scales in favor of apoptosis and causes cell death[54]. Additionally, prior research revealed that the strong ERS activator pterostilbene caused cancer cells to undergo apoptosis-related cell death by triggering ERS[56]. According to Ma et al.[7], pterostilbene therapy could enhance apoptosis in lung cancer PC9 and A549 cells by elevating p-PERK, ATF4, and CHOP levels, which would then cause ER Ca^{2+} to efflux into the cytoplasm and boost ERS activation. Additionally, pterostilbene elevated the levels of DR4 and DR5, triggered the production of reactive oxygen species (ROS), activated ERK1/2 and p38, upregulated CHOP, and eventually amplified the mortality caused by TRAIL in triple-negative breast cancer cells that were resistant to TRAIL[53]. Pterostilbene has been shown in experiments to cause apoptosis in EC109 and TE1 cells that have esophageal cancer by upregulating the levels of GRP78, p-PERK, ATF4, and CHOP[44]. Additionally, pterostilbene caused an imbalance in redox homeostasis, which in turn caused ERS and apoptosis. As illustrated in the Fig. 5, pterostilbene may therefore be an anticancer medication for cancer therapy since the data above suggest that it can encourage the apoptosis of cancer cells.

3.2.4 *p53, NF-κB and MAPK pathway*

Moreover, pterostilbene's ability to modulate key signaling pathways such as NF-κB, MAPK, and p53 plays a crucial role in its pro-apoptotic effects. By suppressing NF-κB, pterostilbene suppresses the transcription of anti-apoptotic genes, while activation of p53 enhances the expression of pro-apoptotic targets, creating a dual-pronged attack on cancer cell survival.

The p53 pathway is a significant tumor suppressor pathways that control cell cycle arrest, DNA repair, apoptosis, and senescence among cell stress or DNA damage. Specifically, the *TP53* gene encodes the protein p53, which functions as a transcription factor and is often nicknamed the 'guardian of the genome'[57]. Upon activation, p53 stimulates the target genes' expression, including p21, which inactivates cyclin-dependent kinases (CDKs); thus, the cell cycle is halted at the G1/S stage. If the damage is beyond repair, p53 activates apoptosis by provoking the proteins that make body cells express Bax and repress the death-suppressing proteins called Bcl-2. Hence, p53 is involved in the control of apoptosis, autophagy, metabolic balance, and other cellular processes[58]. Pterostilbene promotes apoptosis by activating the p53 pathway in breast cancer cells[59]. Another possible mechanism of pterostilbene is to modulate oxidative stress and intracellular lipid deposition. Oxidative stress inhibits PI3K activation, promoting Akt phosphorylation, upregulating p53 expression, activating Caspase-9 and Caspase-3, and lowering the Bcl-2 to Bax ratio, all which are reversed by pterostilbene treatment[60]. The effects of pterostilbene on human lung cancer cells that induce apoptosis were examined in a different study. It was discovered that the administration of pterostilbene induced apoptosis in gastric cancer cells, concomitant with p53 expression increase and the activation of downstream apoptotic pathways[61].

Kawakami et al.[62] reported that pterostilbene inhibits NF-κB activation in human leukemia cells, leading to apoptosis induction. They found that pterostilbene suppresses NF-κB-regulated anti-apoptotic genes and promotes apoptosis through downregulation of NF-κB signaling. It inhibits the phosphorylation and degradation of IκBα, hence, the NF-κB does not enter the nucleus to enhance inflammation, secretion of pro-inflammatory cytokines, tumor survival proteins such as Bcl-2, and promoters of angiogenesis and metastasis. This modulation inhibits cancer cell growth and causes cancer cell death, demonstrating the possibility of pterostilbene as an anti-cancer agent on NF-κB mediated pathways[62].

The MAPK pathway regulates cell division, proliferation, survival, and apoptosis, all of which are vital components of the pathophysiology of cancer. ERK1/2, JNKs, and p38 are among the subfamilies that make up MAPKs. The downstream effector of the pathway is ERK, which has been documented as one of the most important kinases for various cellular functions through phosphorylation and activation of many transcription factors like c-Myc, NF-κB, and ELK-1[63]. The overexpression and downregulation data regarding the regulation of ERK1/2 by pterostilbene are in line with its well-established dual role in cancer[64]. Gao et al.[64] demonstrated that pterostilbene modulates the MAPK signaling pathway in human glioma cells. They found that pterostilbene inhibits ERK phosphorylation, which is involved in cell proliferation and survival, and induces apoptosis through MAPK pathway regulation.

3.3 *Pterostilbene's effect on cancer cell autophagy*

One of the most conserved biological processes is autophagy, which breaks down and recycles proteins and organelles, among other components of the cell. By eliminating harmed or defective cellular components and supplying vital nutrients to cells under stressful circumstances, such as nutritional restriction, hypoxia, or exposure to toxins, it plays a critical role in preserving cellular homeostasis. Depending on a number of variables, including tumor type, stage, and microenvironment, autophagy in cancer can have both tumor-suppressive and tumor-promoting effects[65]. During the initial phase of cancer development, autophagy helps in avoiding the deposition of deleterious components known for breaching programming, hence, instabilities. On the other hand, in larger, more developed cancers, autophagy supports cancer cell survival by providing nutrients and biomolecules during cytostress, including hypoxia and nutrient deprivation.

Pterostilbene is known to have the ability to cause autophagy in cancer cells, which has also been found to be one of the mechanisms of action in treating cancers. The PI3K/AKT/mTOR pathway was another significant point in regulation by pterostilbene for controlling the autophagy of a cell and its metabolism. There was evidence that the mTOR pathway was an inhibitory pathway for autophagy[66]. For example, in the experimental murine models of bladder and oral cancers, pterostilbene upregulated the autophagy levels with an augmentation in LC3 II/I and Beclin 1 proteins to induce apoptosis[41]. According to Chen et al.[67] pterostilbene causes autophagy activation in pancreatic cancer cells by blocking the mTOR pathway. They discovered that pterostilbene's anticancer effects are partly attributed to its inhibition of mTOR signaling and activation of autophagy. An essential function of the AMP-activated protein kinase (AMPK) pathway is to control the induction of autophagy and the maintenance of cellular energy balance. Autophagy is a cytoprotective mechanism that can be induced by ER stress. It has been demonstrated that pterostilbene causes autophagy and ER stress in a variety of cancer cell lines. According to Musial et al.[68] pterostilbene causes human leukemia cells to undergo ER stress-mediated autophagy, which ultimately results in cell death. According to Wang et al.[69], pterostilbene induces autophagy *via* p62 downregulation, which results in increased expression of endogenous Beclin-1, autophagy-related protein 5, 7 and 12 (ATG5, ATG7, ATG12), microtubule-associated protein 1A/1B-light chain 3-II (LC3-II), and increases in LC3-I. This inhibits cell proliferation and causes S-phase cell cycle arrest in human cholangiocarcinoma cells. The authors report that pterostilbene can cause apoptosis and cell cycle arrest in Bcap-37 and MCF-7 breast cancer cell lines, as well as autophagy, as demonstrated by increases in LC3-I and LC3-II[70]. Similarly, Lin et al.[71], find that pterostilbene induces cell cycle arrest and apoptosis in human oral cancer cells SAS and OECM-1, inhibiting their proliferation. It also promoted autophagy *via* controlling the activation of JNK1/2 and the inhibition of Akt, ERK1/2, and p38, as shown by increases in Beclin-1, LC3-II, and LC3-I. It is noteworthy that pterostilbene suppresses the development of hepatocellular carcinoma cells through an autophagy-dependent p-eIF2α/ATF4/LC-3 pathway and ER stress without causing apoptosis[72]. Similarly, in another study, pterostilbene suppressed cell viability and the autophagy of cancer cells. The RNA-Seq investigation showed that pterostilbene decreased the expression of *ATM/ATR*, *HIF-1*, *PI3K*, *RB1CC*, *TBK1*, and mitochondria-related genes, causing death and autophagy in cisplatin-resistant gastric cells[73]. Additionally, it has been demonstrated that pterostilbene causes autophagy in tumor cells, which influences a type of programmed cell death or prevents the growth of tumors and the development of malignant transformation (Fig. 6).

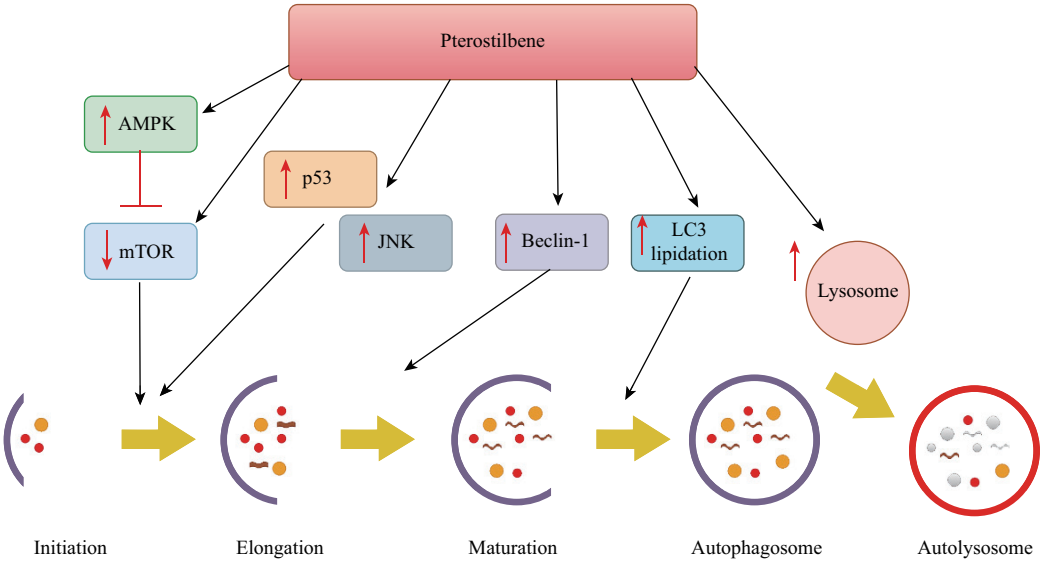

Fig. 6 Effect of pterostilbene on cancer cell autophagy.

In addition, the antioxidant activity of pterostilbene can affect autophagy by controlling the levels of oxidative stress, which are crucial initiators of autophagic responses. Pterostilbene indirectly affects autophagy and its associated pathways by reducing ROS or altering mitochondrial function. ROS promotes as well as inhibits tumors in cancer. Pterostilbene alters ROS-mediated signaling pathways, causing cancer cells to undergo autophagy induction and apoptosis *via* induction of ROS generation and activation of autophagy in breast cancer cells[74]. In conclusion, the modulation of autophagy by pterostilbene is the critical mechanism of its anticancer action. Pterostilbene is promising in targeting the critical regulators of autophagy, and thereby modulating its cross-talk with apoptosis to interfere with tumor cell survival.

3.4 Pterostilbene's effect on cancer cell cycle arrest

Uncontrolled cell proliferation is the primary feature of a tumor. One of the most important contributing factors is the dysregulation of cell cycle checkpoints, which allows cells to proliferate uncontrollably, contributing to tumorigenesis. The major checkpoints in the cell cycle are G1/S, G2/M, and the metaphase/anaphase transition, where cellular integrity is monitored before proceeding to the next phase. Therefore, stopping the cell cycle in cancerous cells may prevent more cancer during the carcinogenesis process[75].

In a study, pterostilbene revealed promising preventive effects against chemotherapy-induced side effects, and the compound also exhibited promising potential in altering the cell cycle functions in cancer cells through the procedure of cell cycle arrest. To date, pterostilbene has been shown to influence different cell cycle regulatory proteins, most of which are in the G1/S and G2/M phases. Through this bioactivity, pterostilbene disrupts the regular cell division cycle and impairs cancer cell proliferation[46].

In the G1 phase, CDKs, particularly CDK4 and CDK6, in complex with cyclin D, phosphorylate the retinoblastoma protein (Rb). Phosphorylation of Rb releases the E2F transcription factors, which then promote the expression of genes required for DNA replication, facilitating the transition to the S phase. Research has demonstrated that pterostilbene can downregulate the levels of cyclin-dependent kinase in cyclin A, cyclin E, CDK2, CDK4, and CDK6, which are linked to Rb phosphorylation and cause HL-60 gastric carcinoma cell G1 arrest[71]. This disruption results in the retention of Rb-E2F binding, preventing E2F-mediated gene transcription and arresting the cell in the G1 phase. Additionally, pterostilbene can upregulate the expression of a cell-intrinsic checkpoint and repair response protein, p53, p21, p27, and p16[71]. Tan et al.[76] demonstrated that downregulated cyclin A and cyclin E, together with upregulated p21 and p27 expression, were responsible for the accumulation of S phase in H520 lung squamous carcinoma cells induced by pterostilbene. As a result, pterostilbene effectively halts the progression of cancer cells from the G1 to the S phase, leading to a reduction in cellular proliferation.

In addition, pterostilbene targets the G2/M phase, where the cell makes sure that DNA has been replicated accurately before entering into the mitotic phase. This checkpoint is regulated by cyclin B and CDK 1, which form a complex to drive the cell into the mitotic phase. Pterostilbene has inhibited cyclin B protein level and CDK1 activity to suppress the cell cycle progression at the G2/M phase. This delay allows cells to fix DNA injury or, in cases of irreparable damage, to undergo programmed cell death and apoptosis[77].

Pterostilbene was found to limit the growth of prostate cancer DU145 and 22Rv1 cell lines by lowering the expression of miR-17, miR-21a, and miR-106a/b. This resulted in the restoration of the expression of the tumor suppressor phosphatase and tensin homolog (PTEN). In this study, pterostilbene also inhibited the growth of tumors by lowering the levels of circulating miR-17-5p and miR-106a-5p and by raising PTEN in the xenograft model[78]. PTEN can regulate the cell cycle through a variety of routes, most likely by controlling the PI3K/AKT pathway. It has been discovered that pterostilbene inhibits the PI3K/Akt/mTOR signaling pathway, which induces apoptosis and cell cycle arrest in the G0/G1 phase of the mantle cell lymphoma JeKo-1 and Granta-519 cell lines[79]. Additionally, it was discovered that pterostilbene inhibited the proliferation of A549 and NSCLC lung cancer cells by activating the checkpoint kinases 1/2 (CHK1/2) and ataxia telangiectasia mutant (ATM) pathways upstream of p53[80].

Cell cycle arrest is often mediated by the tumor suppressor protein p53, which regulates the expression of genes involved in cell cycle control. Pterostilbene activates the p53 pathway in cancer cells, resulting in p53-mediated cell cycle arrest in breast cancer cells by upregulating the expression of p53 and its downstream target genes[61]. According to Sanaei et al.[81], pterostilbene inhibits CDK activity, causing cancer cells to enter a cell cycle arrest and reducing the proliferation of cancer cells in human prostate cancer cells. Furthermore, pterostilbene alters the MAPK signaling pathway in cancer cells, resulting in cell cycle arrest and reducing the growth of cancer cells[64]. The notch signaling pathway regulates cell fate decisions, including cell cycle progression and proliferation. Pterostilbene has been reported to modulate Notch signaling in cancer cells. Liu et al.[74] investigated the effect of pterostilbene on cell cycle regulation in lung cancer cells and found that it inhibits notch signaling, leading to cell cycle arrest and inhibition of cancer cell growth. In conclusion, pterostilbene as presented in Fig. 7, can significantly aid in cell cycle arrest and inhibit the growth and spread of cancer by activating a number of signaling pathways

3.5 Pterostilbene in the progression stage of carcinogenesis

Cancer progression and metastasis are the primary factors responsible for the high mortality rate associated with cancer. When carcinogenesis is at its progressive stage, around 90% of cancer patient deaths take place. Molecularly, tumor progression is defined as the ability of cancer cells to relentlessly proliferate, while metastasis is the process by which cancer cells disseminate to structures away from the primary site. Both processes are intricate and driven by numerous molecular intermediates, such as the alteration in gene profile, differential cell signaling, and changes in the ECM. A plentiful supply of nutrients facilitates the invasion of neighboring tissues by malignant cells, which then proceed to migrate from the main tumor to distant organs and multiply at sites of metastasis[48]. It is more challenging in cancer, mostly because it makes the disease more aggressive and resistant to conventional treatments. Thus, aiming at the processes of cancer progression and metastasis itself is considered to be one of the key elements of anticancer therapy.

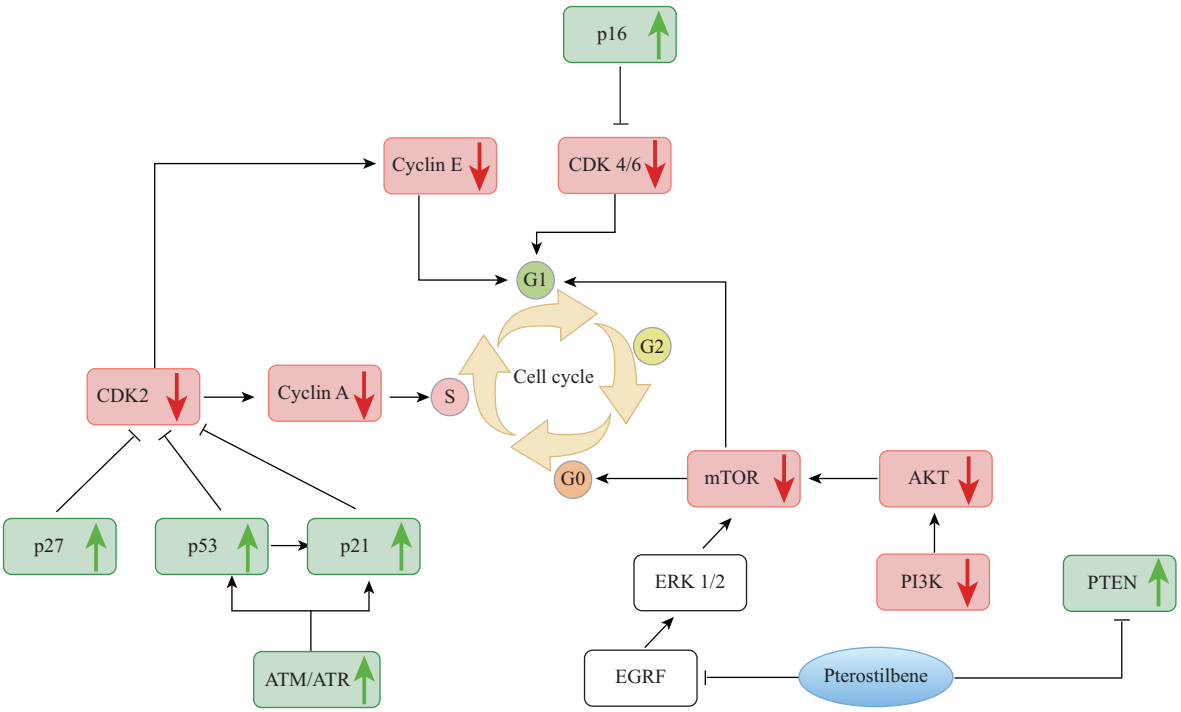

Fig. 7 Effect of pterostilbene on cancer cell cycle arrest.

Pterostilbene has been shown to inhibit cancer progression and metastasis and to help fight against angiogenesis. Since angiogenesis creates the vast capillary network required to supply oxygen and nutrients to tumors and eliminate metabolic waste from them, it is essential for the growth and metastasis of invasive tumors. To slow the spread of cancer, one chemotherapeutic tactic is to control tumor-associated angiogenesis. The process of angiogenesis is regulated by a variety of cytokines (inflammatory microenvironment) and anti-angiogenic factors, with VEGF being the primary positive regulatory factor. Pterostilbene appears to be able to inhibit angiogenesis, based on substantial evidence. Pterostilbene has been shown in a study to reduce the production of VEGF in SK-MEL-2 human melanoma cell lines[71]. Pterostilbene inhibits VEGF, IL-1β, and HIF-1α, three proangiogenic molecules linked to MTA1, which decreases angiogenesis in PC3M prostate cancer cells[82]. Furthermore, pterostilbene inhibits angiogenesis by targeting c-Met, the inactivation of which in turn reduces angiogenesis, invasion, and perivascular migration in breast cancer 231BrM cells *via* means of IL-8 and CXCL1-mediated CXCR1 signaling[83].

Many microenvironmental elements, including extracellular matrices (ECMs), matrix metalloproteinases (MMPs), and growth factors for tumor cells, influence the invasion and metastasis of tumor cells. Pterostilbene has been demonstrated to inhibit NF-κB and AP-1 activity by downregulating PKC, EGF, and VEGF. This, in turn, blocks the phosphorylation of MAPK and the PI3K/AKT pathway, decreasing *MMP-9* gene expression and preventing TPA-mediated HepG 2 cell line metastasis[84]. Pterostilbene has also been shown to decrease MMP-2 and u-PA expression, block DNA-binding activities on MMP-2 and u-PA promoters, inhibit CREB, NF-κB, and SP-1 expression, and ultimately suppress the effects on oral cancer SCC-9 cell line invasion and migration[85]. Furthermore, by upregulating E-Cadherin and downregulating *N*-cadherin, Twist, Snail, Slug, vimentin, ZEB1, and ZEB2 expression in MCF7 breast cancer cells, pterostilbene can decrease EMT and migration[86]. Similarly, studies in prostate cancer indicate that pterostilbene inhibits MTA1[87]. These results imply that pterostilbene controls several signaling molecules, which may contribute to its anti-angiogenesis and anti-invasion/metastasis activities.

Also, pterostilbene impacts pathways related to the regulation of cell migration and invasion of such cells. Among the Rho family of GTPases, RhoA, Rac1, and Cdc42 are involved in the control of cytoskeletal processes and cell migration. Pterostilbene has been known to inhibit these Rho GTPases, thus decreasing cancer cell motility and invasion. The Rho signaling pathway can therefore be inhibited to avoid the formation of lamellipodia and filopodia, which are structures that facilitate movements during metastatic processes as identified by Carrano et al.[88].

The immunomodulatory property of pterostilbene also contributes to suppressing cancer development and metastasis. Various inflammatory cells and cytokines in the tumor microenvironment also stimulate metastasis through cell migration, invasion, and angiogenesis. Pterostilbene modulates the abilities of inflammatory mediators, including NF-κB and COX-2, of which inhibitions decrease the inflammatory signaling associated with metastasis[71].

In summary, pterostilbene can effectively suppress cancer progression and metastasis by acting on various molecular targets. Through the modulation of some of the signaling pathways that play a part in cell adhesion, migration, ECM breakdown, as well as EMT, the cancer cell's capacity to metastasize and form secondary colonies is confined by pterostilbene. As an inhibitor of MMPs, integrin, Rho G protein, and EMT transcription factor, it may have significant potential for the prevention of metastatic spread as an adjunct in cancer therapy.

4. Pterostilbene and cancer types

However, to fully appreciate the anticancer efficacy of pterostilbene, many studies have been made *in vitro* and *in vivo,* dealing with different types of cancer. These have explained the molecular target, the signals altered, and the therapeutic outcomes. Mainly, *in vitro* experiments are aimed at evaluating the effects of candidates on cytotoxicity, cell cycle distribution, apoptosis, and the abilities of migration and invasion in cancer cells. In contrast, *in vivo* models assess its effectiveness in inhibiting tumor formation, metastasis, angiogenesis, pharmacokinetics, as well as toxicity.

Table 2 summarizes key findings from recent *in vitro* and *in vivo* studies of pterostilbene in different cancer types, highlighting its mechanisms of action and therapeutic potential.

Table 2
Key findings from recent *in vitro* and *in vivo* studies of pterostilbene in different cancer types.

Cancer type	Study model	Dosage	Effect	References
Breast cancer	Human ER-positive, T-47D cells and triple-negative MDA-MB-231 cells	80–150 μmol/L	Induce apoptosis, downregulate protein expressions of mTOR, *β*-catenin, mutant p53, antiapoptotic protein, induce Caspase-3 activity	[51]
	Human MCF7 and MDA-MB231 cells	63 μg/mL	Ameliorate antiproliferative, proapoptotic and oxidativestress potentials	[89]
	mouse breast cancer cell lines (EMT6 and 4T1), mouse mammary epithelial cells (HC11)	40 μmol/L	Induce pyroptosis by inhibiting glycolysis	[90]
	ER positive MCF-7 cells, SK-BR 3 cells, MDA-MB-468	100 μmol/L	Inhibit the phosphorylation of AKT and mTOR, leading to reduce cell proliferation and increase apoptosis	[91]
	Human breast cancer cell lines MCF-7, MDA-MB-231, MDA-MB-468, murine breast cancer cell line 4T1	> 2.5 μmol/L	Inhibit the nuclear translocation of *β*-catenin to inactivate the expression of target protein of c-MYC, CyclinD1, CD44 and MMPs.	[92]
	Human mammary gland epithelial adenocarcinoma cell line (MDA-MB-231)	10 and 25 μmol/L	Inhibition of downstream AP1 activation and cell cycle protein regulation	[93]
	Female nude mice (BALB/cAJcl-nu/nu), 5 weeks old, *n* = 6	0.1% (*m*/*m*)	Inhibit the phosphorylation of AKT and mTOR, leading to reduce cell proliferation and increase apoptosis	[91]
	Severe Combined Immunodeficient (SCID), female mice, 4 weeks old, *n* = 5	–	Inhibit downstream AP1 activation and cell cycle protein regulation	[93]
Lung cancer	Human NSCLC cells (PC9 and A549 cells)	60 μmol/L	Suppress ERS desensitizes, induce ERS-pro-apoptotic mechanisms	[7]
	Human lung cell lines NCI-H520 and NCI-H226,	50 μmol/L	Cause cell cycle arrest, induce apoptosis	[76]
	BALB/c mice, 5 weeks old, *n* = 6	50 mg/kg	Induce cell cycle arrest in the G1-S phase transition *via* the downregulation of cyclin D1 and E2 and the upregulation of p53 and its downstream effectors, p21, resulting in cell proliferation inhibition and apoptosis induction	[61]
	Specific pathogen-free male Sprague Dawley rats	25 and 50 mg/kg	Protective mechanism through jak2/stat3 pathway, inhibit inflammation and apoptosis	[94]
	Male BALB/c mice, 4 weeks old, *n* = 6	10, 20 and 40 mg/kg	Improve the antioxidant capacity of lung tissue and reduce the inflammatory cytokines induced by LPS , and play a protective in LPS-induced ALI through regulating Nrf2/HO-1 and NF-κB signaling pathways	[95]
	Female BALB/c athymic nude mice, 6 weeks old, *n* = 6	50 mg/kg	Cause cell cycle arrest, induce apoptosis	[76]
Colorectal cancer	COLO205, HCT116, SW480 cells	20 μmol/L	Alleviate adiposity-induced metastasis by inhibiting cell migration through downregulating *FABP5* gene expression by suppressing multiple signaling pathways	[96]
	Human colon adenocarcinoma HT-29 cell line	≥ 10 μmol/L	Downregulate of the STAT3 and AKT kinase pathways	[97]
	Human gastric cancer cell lines HGC-27 and MKN-45	–	Anti-cancer effect by STAT3 activation, validate JAK2/STAT3 signaling pathway	[42]
	BABLc/nude mice, 18–20 g, 5 weeks old	100 and 500 mg/kg	Inhibited tumor development	[43]

Table 2 (*Continued*)

Cancer type	Study model	Dosage	Effect	References
Prostate cancer	Human ovarian cancer cell line SKOV3 and Caov-3	37.5–300.0 μm	Reduces proliferation and migration in ovarian cancer cells involving inhibition of the STAT3 pathway	[98]
Mantle cell lymphoma	Human MCL cell lines JeKo-1 and Granta-519	0–80 μmol/L	Expression of p-PI3K/p-Akt/p-mTOR/p-p70S6K was suppressed p-mTOR was decreased	[79]
Cervical cancer	HeLA adherent and stem-like cells	20 and 40 μmol/L	Inhibit growth, viability and migration of HeLa adherent cells Downregulation of Bcl-2 and Bcl-xL	[33]

Note: - , Not specified; LPS, lipopolysaccharides.

Breast cancer is among the common cancer types on the global scene. Pterostilbene has a great potential to influence key molecular targets effective for breast cancer development. Some of the latter have indicated that pterostilbene acts on the tumor growth by inhibition of the aforementioned PI3K/AKT/mTOR signal cascade. For example, by reducing the phosphorylation of the AKT protein, pterostilbene reduces the growth of cancer cells and induces apoptosis[79]. Data suggest that pterostilbene promotes a robust yet long-lasting ERK activation leading to G0/G1 cell cycle arrest in breast cancer cells[91]. In the experiment, pterostilbene suppressed mTOR, *β*-catenin, mutant p53, and anti-apoptosis protein expression and increased Caspase-3 activity in breast cancer cell lines, suggesting that it induced apoptosis[51].

In lung cancer, it has also been suggested that pterostilbene suppresses tumor growth mainly through the inhibition of the MAPK/ERK signaling pathway. Thereby, inhibiting ERK phosphorylation implies tumor growth and triggers apoptosis[7]. However, in an *in vivo* study, pterostilbene affects the JAK/STAT signaling pathway and suppresses pro-survival genes like Bcl-2 and c-Myc[94]. Studies have also pointed out that it helps in controlling oxidative stress and maintains the balance of oxidation at the cellular level[7]. Pterostilbene may, therefore, exercise a modulating effect over the Nrf2/HO-1 and NF-κB signaling pathways to increase the antioxidant capacity of lung tissue, reverse LPS as well, and reduce the inflammatory cytokines contributing to lipopolysaccharide-induced acute lung injury (LALIT)[95]. These mechanisms enable pterostilbene to be considered as a good adjuvant to lung cancer treatment.

Chronic inflammation of colorectal cells and alterations in cell division cycles are significant in the tumor development of colorectal cancer. Pterostilbene possesses a significant anti-inflammatory effect due to the down-regulation of COX-2 and decreased levels of the pro-inflammatory mediator IL-6, and tumor necrosis factor-α (TNF- α)[74]. It also inhibits the action of STAT3, which is an important factor in inflammation-induced tumorigenesis[99]. Moreover, in an *in vitro* study, pterostilbene exhibits anti-cancer activity by reducing adiposity-promoted metastasis in colorectal cancer by inhibiting cell migration and reducing *FABP5* gene expression by regulating multiple signaling pathways[96]. In another study, Wawszczyk et al.[97] observed that pterostilbene inhibits STAT3 and AKT kinase signaling in HT-29 cells.

Prostate cancer remains a leading cause of cancer-related deaths among men. More recent studies from the same group further elucidated the molecular mechanism of action of pterostilbene and identified the androgen receptor signaling as a putative target in prostate cancer[100]. Pterostilbene suppresses androgen-dependent cancerous cell proliferation through the regulation of androgen receptor expression. Besides, it suppresses the AKT/mTOR signaling, thereby decreasing cell multiplication and increasing cell death. They have also noted the capability of recently used doses in inhibiting the TGF-β/SMAD pathway, considered crucial in EMT and metastasis in advanced PCa[101]. Pterostilbene has been reported to increase the chemosensitivity of PCEC through the inhibition of the proteasome export, drug resistance-associated factors: NF-κB and Hedgehog signaling[19].

Recent studies have pointed to the increased efficacy of pterostilbene in other kinds of cancer, such as pancreatic, liver, and hematologic malignancies. Thus, in pancreatic cancer, pterostilbene targets oncogenic signaling molecular KRAS, decreasing tumor cell proliferation and migratory potential[102]. Experiments published in liver cancer show that resveratrol interferes with the Wnt/*β*-catenin and STAT3 pathway to decrease hepatocellular carcinoma and inflammation[103]. In hematological cancers, pterostilbene triggers apoptosis by activating caspases and also arrests the proliferation of leukemic cells through JAK/STAT pathway inhibition[62]. Pterostilbene has shown high efficiency in treating cervical cancer (20 and 40 μmol/L) in HeLA adherent and stem-like cells. These effects were achieved through inhibiting the growth, viability, and migration of cancer cells and by downregulating anti-apoptotic proteins.

For the moment, there are only 2 clinical trials running where pterostilene is used against specific cancer types. In one trial (NCT03671811), the effectiveness of megestrol acetate, with or without pterostilbene, in treating patients with endometrial cancer undergoing hysterectomy is being investigated. In this phase 2 research, pterostilbene is orally given twice daily, with megestrol acetate for 3 weeks or only megestrol acetate for 3 weeks in the absence of disease progression or unacceptable toxicity. In the other trial (NCT05886673), 2% pterostilbene, 1% silibinin, and 2% nicotinamide riboside are present in the experimental cream formulation. The effectiveness of the cream in relation to radioprotective and radiomitigation effects in the preventive treatment of acute radiation-induced radiodermatitis will be assessed in a multicenter, randomised, controlled clinical trial conducted at 2 hospitals within Valencia's Radiation Oncology service.

5. Comparative and synergistic therapeutic potential of pterostilbene in cancer treatment

5.1 Comparative insights with other natural anticancer compounds

Some natural polyphenols, including flavonoids and stilbenes: pterostilbene, quercetin, curcumin, epigallocatechin gallate (EGCG), resveratrol, and genistein, exhibit good anticancer effects. Despite some similarities in the mechanisms of their action, those compounds

differ in their properties and some cases, have definite limitations in terms of efficacy and applicability.

Pterostilbene, a natural compound related to resveratrol, the active molecule, had an antagonistic effect on numerous signaling pathways like PI3K/AKT/mTOR[79,104], JAK/STAT[42,105], and Wnt/*β*-catenin[92]. These pathways are involved in apoptosis, cell division, cell migration, and protection against cell damage called oxidative stress. In the same manner, Quercetin has some impact on NF-κB[106], MAPK[107], and AMPK[108], facilitating inflammation inhibition and apoptosis enhancement. The active compound of turmeric, Curcumin, inhibits NF-κB signaling[109], JAK/STAT3, and COX-2 signaling[110]. The major catechin identified in green tea is EGCG, which has significant referential antioxidant activity and has anti-cancerous activity due to the regulation of EGFR, MAPK, and VEGF, hence reducing angiogenic metastasis[111]. Resveratrol is a structural analog of pterostilbene but is less lipophilic. It also targets the sirtuins, Wnt/*β*-catenin, and NF-κB pathways, and hence, it is anti-inflammatory, pro-apoptotic, and has anticancer properties[112]. Soy isoflavone genistein chiefly inhibits ERK, Akt, and Wnt signaling and has hopeful prospects in hormone-sensitive carcinoma since it functions as a phytoestrogen[113].

An important issue of these compounds is their solubility, or, to be more precise, their poor bioavailability. As with resveratrol, pterostilbene is lipophilic and allows better membrane permeability; however, its systemic bioavailability is still reduced by the action of metabolism enzymes[16]. Quercetin and curcumin have neuroprotection in multiple pathways, including inhibiting multiple pathways, but suffer from poor systemic bioavailability[114]. Sirtuin activation is another contributing factor gained from resveratrol in aging-related carcinomas, but its short half-life biological activity diminishes its effectiveness[112].

The use of natural compounds in cancer therapy strategies underscores various ways that these agents elicit their actions. However, it makes more sense to look at the big picture and gather information about other compounds, such as quercetin, curcumin, EGCG, resveratrol, and genistein, in the context of their application for cancer treatment.

5.2 Synergistic effects of pterostilbene in radiotherapy and chemotherapy

The potential of pterostilbene as an adjuvant in conventional cancer treatments has gained attention due to its ability to enhance the efficacy of radiotherapy and chemotherapy while mitigating their side effects. Its unique properties, including antioxidant activity, apoptosis induction, and modulation of key signaling pathways, make it a promising candidate for combination therapy in cancer treatment.

One of the major challenges in chemotherapy is the development of drug resistance, which often leads to treatment failure[115]. Pterostilbene has demonstrated the ability to overcome this resistance by targeting multiple oncogenic pathways. Additionally, pterostilbene can suppress multidrug resistance proteins, which are responsible for drug efflux and reduced intracellular drug accumulation, leading to enhanced cytotoxicity of agents such as cisplatin, doxorubicin, and 5-fluorouracil. For instance, patients with pancreatic ductal adenocarcinoma have poor outcomes and substantial mortality rates due to gemcitabine treatment resistance. By downregulating RAGE/PI3K/Akt signaling, pterostilbene suppressed the expression of multidrug resistance protein 1 and caused S-phase cell cycle arrest, apoptosis, and autophagic cell death in MIA PaCa-2 and MIA PaCa-2 GEMR cells. Pterostilbene may, therefore, be essential in modulating multidrug resistance for the treatment of pancreatic ductal adenocarcinoma, according to the findings of these investigations[116]. Moreover, among the undruggable cancer targets are RAS oncoproteins. Through RAS-related autophagy and cell senescence pathways, pterostilbene was found to sensitize cisplatin-resistant bladder cancer cells with HRAS mutations. This finding raised the possibility that pterostilbene could be used as a chemotherapeutic agent to treat human bladder cancer with oncogenic HRAS that is resistant to cisplatin. Based on observations by Chen et al.[41], pterostilbene can be used for regulation in cancer therapy when combined with the traditional chemotherapy drugs (such as Gemcitabine and Cisplatin).

Radiotherapy remains a cornerstone in cancer treatment, yet radioresistance in tumor cells often limits its effectiveness[117]. Pterostilbene has been reported to function as a radiosensitizer by increasing oxidative stress within cancer cells while protecting normal cells from radiation-induced damage. Studies have shown that pterostilbene enhances the generation of ROS in cancer cells, promoting DNA damage and increasing sensitivity to ionizing radiation[118]. While preclinical studies have demonstrated the promise of pterostilbene in combination with chemotherapy and radiotherapy, further research is required to translate these findings into clinical practice. Future studies should focus on optimizing dosage regimens, evaluating synergistic effects in different cancer models, and conducting clinical trials to validate their efficacy in combination therapies. The use of nano-formulated pterostilbene may further enhance its bioavailability and therapeutic benefits when used alongside standard cancer treatments.

6. Biotransformations and bioavailability of pterostilbene

Pterostilbene has garnered significant attention for its anticancer and antioxidant properties. However, its clinical application is limited by challenges related to bioavailability and metabolic transformations within the body. These factors influence its pharmacokinetics and therapeutic efficacy, necessitating a deeper understanding of its biotransformations and the development of strategies to enhance its bioavailability.

6.1 Biotransformations of pterostilbene

When administered orally, the major metabolism of pterostilbene is in the form of phase I and phase II metabolism. In contrast to the structural substitute, resveratrol, containing hydroxyl groups, pterostilbene contains methoxy groups that enhance the stability of the compound. However, this methylation decreases the ability of the compound to metabolize in phase I metabolism, leading to enhanced metabolic stability[119]. Like with most phytochemicals, in phase II metabolism, pterostilbene undergoes conjugation reactions such as glucuronidation and sulfation. These reactions, mainly catalyzed by enzymes, including UDP-glucuronosyltransferase (UGT) and sulfotransferase (SULT), lead to the generation of pterostilbene glucuronide and sulfate derivatives. Although these conjugates are more water-soluble, they limit the quantity of the active pterostilbene form in the systemic circulation[17].

6.2 Bioavailability challenges and strategies for enhancement

Pterostilbene is greater in lipophilicity compared to resveratrol, but it provides low systemic bioavailability because it undergoes first-pass metabolism expeditiously. Research showed that less than 1% of the active compound form of pterostilbene was absorbed in the bloodstream after being ingested orally. This limited its ability to exert a therapeutic effect and remain effective within a disease model that requires constant systemic presence. The poor biopharmaceutical properties that lead to low bioavailability include poor water solubility, rapid enzymatic degradation, and low rate of absorption in the GI tract[16].

This led the research toward improving pterostilbene bioavailability in 2 directions: drug delivery strategies and changes in its structure. The nano drug delivery system, which means the compound incorporation of pterostilbene in nanoparticles, liposomes, or solid lipid nanoparticles, improves the bioavailability and stability of the compound. Nano drug carriers have been utilized extensively in tumor therapy because they exhibit targeted and delayed release characteristics, a variety of dosage forms, and the ability to be administered in numerous ways to minimize side effects. Recent years have seen a surge in interest in biomimetic nanocarriers, particularly red blood cells, which have emerged as innovative drug delivery vehicles for tumor treatment. Erythrocyte membranes, for instance, have garnered increased interest lately as bionic nano-drug delivery systems[120].

These delivery systems protect pterostilbene from rapid degradation in the gastrointestinal tract, facilitate controlled release, and improve systemic circulation time, ultimately increasing its bioavailability and therapeutic potential[121]. For instance, Zou et al.[122] loaded pterostilbene into nanoparticles using soybean lecithin and polyethylene glycol succinate. The results showed that the anti-cancer effects of pterostilbene were significantly higher in breast cancer cell models *in vitro*. Further, their *in vivo* studies supported these results, indicating that a nano-drug delivery system can enhance the bioavailability of pterostilbene. Similarly, ethoniosomal formulation with pterostilbene showed potential application as a nano-carrier in lung cancer *in vitro* and *in vivo*[123]. Moreover, pterostilbene nano capsules successfully enhanced the therapeutic efficacy of pterostilbene in HepG2 liver cancer cell lines[124]. Taken together, using different strategies to improve oral bioavailability of pterostilbene, the efficiency of treatment can be enhanced successfully.

Another key approach involves prodrug development and structural modifications to enhance the pharmacokinetic properties of pterostilbene. These prodrugs are designed to release the active type of pterostilbene in the bloodstream after it has been absorbed for better access to the compound[120]. For instance, pterostilbene is a biflavone that has low water solubility and stability. Nevertheless, it can form inclusion complexes with cyclodextrins, which are cyclic oligosaccharides. This has been of immense benefit in the improvement of the absorption and pharmacokinetic properties of the compound[27]. In other words, pterostilbene bioavailability can be increased by bio-enhancers such as piperine or quercetin due to its decreased metabolic rate. These compounds also influence some enzymes that break down pterostilbene and will ensure that a significant concentration reaches the tissues of interest[125].

The bioavailability issues of pterostilbene need to be addressed in order to realize the therapeutic benefit that comes with it. Because of good absorption and biotransformation routes, researchers are aware of its enhancement for systemic availability and effectiveness through newer delivery systems. Such advancements are critical to achieving the biological potential observed in preclinical studies of pterostilbene and its chemopreventive and chemotherapeutic applications in cancer.

7. Future directions

Although pterostilbene has shown exciting promise in preclinical trials, there are still critical shortcomings in understanding its full potential as an anticancer agent. Future research should be specifically targeted to fill these gaps to optimize its potential applications in the clinical setting and improve patient outcomes. Bioavailability issues of pterostilbene were solved to realize the therapeutic gain associated with it. Due to its good absorption and biotransformation routes understanding, researchers understand its enhancement for the systemic availability and effectiveness through newer delivery systems. Such advancements are critical in achieving the biological potential observed in preclinical studies of pterostilbene as well as its chemopreventive and chemotherapeutic applications in cancer.

We believe that more research needs to be done on the possibility of pterostilbene as a cofactor in combination therapies. Researchers need to investigate how it works with other medications like chemo, radiation, and immunotherapy. Of particular interest is the compound's direct assault on the mechanisms of drug resistance, which poses a great threat to current cancer therapies. Activation of mechanistic targets that could influence drug resistance pathways by pterostilbene, such as the PI3K/AKT/mTOR signaling, may improve the outcome of traditional antidotes.

Future research on pterostilbene’s anticancer potential could incorporate Patient-Derived Xenograft (PDX) models to better evaluate its therapeutic efficacy and translational potential. PDX models, which maintain the genetic and histopathological characteristics of patient tumors, provide a more accurate representation of human cancer biology compared to conventional cell lines. By utilizing PDX models, researchers can assess pterostilbene’s tumor-suppressive effects in a personalized setting, investigate mechanisms of drug resistance, and explore its potential in combination therapies. This approach will enhance the clinical relevance of preclinical findings and support the development of pterostilbene-based cancer treatments[126].

Clinical trials are essential to validate the preclinical findings and to address practical considerations such as dosage optimization, safety profiles, and pharmacokinetics. Most of the studies conducted on pterostilbene have been limited to *in vitro* or animal models, and there is a need for strong human trials to establish its therapeutic potential. In addition, its effectiveness can be evaluated as an individual therapy and as a component of treatment regimens to understand its usefulness throughout the different stages of cancer and different types of cancer.

Yet another critical challenge is that pterostilbene has very low solubility and, hence, poor bioavailability. Although pterostilbene has a greater pharmacological activity than resveratrol, pterostilbene is quickly metabolized and does not achieve significant systemic levels. New methods of delivery, including nanoparticles, liposomes, hydrogels, and prodrug strategies, are effective in improving its

solubility as well as its bioavailability. This covers the issues of growth in manufacturing, efficiency of differentiated formulations, and bureaucratic challenges related to products of natural origin. Also, other patient-related factors like the patient's genotype, tumor environment, and stage of cancer will be valuable in the development of personalized pterostilbene therapy.

However, the problems arising out of prospects for clinical application of pterostilbene are the key to its application in oncology. This includes the potential for high throughput, the lowest cost of new formulations, and the legal demands of natural products. In addition, it will be mandatory to introduce patient-related parameters of pterostilbene treatment; genetic variability, tumor microenvironment, and cancer stage. Concerning these future trends and research questions, the researchers are in a good position to set pace in the realization of pterostilbene into mainstream cancer therapies as a natural remedy.

8. Conclusion

In conclusion, this review, buttressed by synthesized evidence of published works, has sought to explain comprehensively the molecular basis upon which pterostilbene impacts cancer cells and how it influences key signaling pathways, including PI3K/AKT/mTOR, NF-κB, and MAPK/ERK pathways. According to the data given, the survival of pterostilbene offers a prospect for inducing apoptosis, autophagy, and cell cycle arrest, thereby preventing the growth of cancer and its spread. The preclinical data are encouraging, though there are difficulties such as low bioavailability and a requirement for further clinical evidence. Further studies should be aimed at overcoming these limitations, investigating the effects of the combined application of pterostilbene with other drugs, as well as to create new effective delivery systems for this compound. In conclusion, this present review will enhance the understanding of anti-cancer treatment through pterostilbene and provide an encouraging natural constituent for future use.

Conflict of interest statement

Baojun Xu is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare that there are no conflicts of interest.

Acknowledgments

This project was jointly supported by two grants (UICR0400015-24B and UICR0400016-24B) from Beijing Normal-Hong Kong Baptist University, China.

References

[1] F. Bray, M. Laversanne, H. Sung, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA 74 (2024) 229-263. https://doi.org/10.3322/caac.21834

[2] A. Mustapha, A. Ismail, S.U. Abdullahi, et al., Cancer chemotherapy: a review update of the mechanisms of actions, prospects and associated problems, BIOMED Nat. Appl. Sci. 1 (2021) 1-19.

[3] F. Davodabadi, S.F. Sajjadi, M. Sarhadi, et al., Cancer chemotherapy resistance: mechanisms and recent breakthrough in targeted drug delivery, Euro. J. Pharmacol. 958 (2023) 176013. https://doi.org/10.1016/j.ejphar.2023.176013.

[4] M. Sambi, L. Bagheri, M.R. Szewczuk, et al., Current challenges in cancer immunotherapy: multimodal approaches to improve efficacy and patient response rates, J. Oncol. 2019 (2019) 4508794. https://doi.org/10.1155/2019/4508794.

[5] V. Fialková, H. Ďúranová, P. Borotová, et al., Natural stilbenes: their role in colorectal cancer prevention, DNA methylation, and therapy, Nutr. Cancer 76 (2024) 760-788. https://doi.org/10.1080/01635581.2024.2364391.

[6] H.Y. Tsai, C.T. Ho, Y.K. Chen, et al., Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxy pterostilbene, J. Food Drug Anal. 25 (2017) 134-147. https://doi.org/10.1016/j.jfda.2016.07.004.

[7] Z. Ma, Y. Yang, S. Di, et al., Pterostilbene exerts anticancer activity on non-small-cell lung cancer *via* activating endoplasmic reticulum stress, Sci. Rep. 7 (2017) 8091. https://doi.org/10.1038/s41598-017-08547-0.

[8] R. Kosuru, U. Rai, S. Prakash, et al., Promising therapeutic potential of pterostilbene and its mechanistic insight based on preclinical evidence, Eur. J. Pharmacol. 789 (2016) 229-243. https://doi.org/10.1016/j.ejphar.2016.07.046.

[9] E. Obrador, R. Salvador-Palmer, A. Jihad-Jebbar, et al., Pterostilbene in cancer therapy, Antioxidants 10 (2021) 492. https://doi.org/10.3390/antiox10030492.

[10] G. Kaur, R. Kaur, G.K. Sodhi, et al., Stilbenes: a journey from folklore to pharmaceutical innovation, Arch. Microbiol. 206 (2024) 229. https://doi.org/10.1007/s00203-024-03939-z.

[11] S. Cherian, K.M. Hacisayidli, R. Kurian, et al., Therapeutically important bioactive compounds of the genus *Polygonum* L. and their possible interventions in clinical medicine, J. Pharm. Pharmacol. 75 (2023) 301-327. https://doi.org/10.1093/jpp/rgac105.

[12] O. Surien, S.F. Masre, D.F. Basri, et al., Potential chemopreventive role of pterostilbene in its modulation of the apoptosis pathway, Int. J. Mol. Sci. 24 (2023) 9707. https://doi.org/10.3390/ijms24119707.

[13] P. Jeandet, E. Sobarzo-Sánchez, A.S. Silva, et al., Whole-cell biocatalytic, enzymatic and green chemistry methods for the production of resveratrol and its derivatives, Biotechnol. Adv. 39 (2020) 107461. https://doi.org/10.1016/j.biotechadv.2019.107461.

[14] C. Medrano-Padial, A.I. Prieto, M. Puerto, et al., Toxicological evaluation of piceatannol, pterostilbene, and ε-viniferin for their potential use in the food industry: a review, Foods 10 (2021) 592. https://doi.org/10.3390/foods10030592.

[15] B.J. Dutta, P.S. Rakshe, N. Maurya, et al., Unlocking the therapeutic potential of natural stilbene: exploring pterostilbene as a powerful ally against aging and cognitive decline, Ageing Res. Rev. 92 (2023) 102125. https://doi.org/10.1016/j.arr.2023.102125.

[16] Y. Liu, Y. You, J. Lu, et al., Recent advances in synthesis, bioactivity, and pharmacokinetics of pterostilbene, an important analog of resveratrol. Molecules 25 (2020) 5166. https://doi.org/10.3390/molecules25215166.

[17] S. Nagarajan, S. Mohandas, K. Ganesan, et al., New insights into dietary pterostilbene: sources, metabolism, and health promotion effects. Molecules 27 (2022) 6316. https://doi.org/10.3390/molecules27196316.

[18] E.W.C. Chan, C.W. Wong, Y.H. Tan, et al., Resveratrol and pterostilbene: a comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties, J. Appl. Pharm. Sci. 9 (2019) 124-129. https://doi.org/10.7324/JAPS.2019.90717.

[19] H. Kim, K.H. Seo, W. Yokoyama, et al., Chemistry of pterostilbene and its metabolic effects, J. Agric. Food Chem. 68 (2020) 12836-12841. https://doi.org/10.1021/acs.jafc.0c00070.

[20] S.O. Duke, Benefits of resveratrol and pterostilbene to crops and their potential nutraceutical value to mammals, Agriculture 12 (2022) 368. https://doi.org/10.3390/agriculture12030368.

[21] J.M. Pezzuto, O. Vang, Natural products for cancer chemoprevention: single compounds and combinations, Springer Int. Publ, Switzerland, 2020. https://doi.org/10.1007/978-3-030-39855-2.

[22] Y. Lu, D. Shao, J. Shi, et al., Strategies for enhancing resveratrol production and the expression of pathway enzymes, Appl. Microbiol. Biotechnol. 100 (2016) 7407-7421. https://doi.org/10.1007/s00253-016-7723-1.

[23] J. Jin, Y. Shan, L. Zhang, et al., Pterostilbene ameliorates fumonisin B1-induced cytotoxic effect by interfering in the activation of JAK/

STAT pathway, Antioxidants 11 (2022) 2360. https://doi.org/10.3390/antiox11122360.

[24] K. Monceaux, M. Gressette, A. Karoui, et al., Ferulic acid, pterostilbene, and tyrosol protect the heart from ER-stress-induced injury by activating SIRT1-dependent deacetylation of eIF2α, Int. J. Mol. Sci. 23 (2022) 6628. https://doi.org/10.3390/ijms23126628.

[25] M. Yi, G. Wang, J. Niu, et al., *Pterostilbene attenuates* the proliferation and differentiation of TNF-α-treated human periodontal ligament stem cells, Exp. Ther. Med. 23 (2022) 304. https://doi.org/10.3892/etm.2022.11233.

[26] M.J. Ruiz, M. Fernández, Y. Picó, et al., Dietary administration of high doses of pterostilbene and quercetin to mice is not toxic, J. Agric. Food Chem. 57 (2009) 3180-3186. https://doi.org/10.1021/jf803579e.

[27] D. Yang, H. Liu, H. Meng, et al., Preparation and physicochemical characterization of inclusion complex of pterostilbene–hydroxypropyl-*β*-cyclodextrin for enhancing the application of pterostilbene in cosmetics, J. Photochem. Photobiol. A Chem. 447 (2024) 115221. https://doi.org/10.1016/j.jphotochem.2023.115221.

[28] D.S. Lacerda, S.E. Bianchi, W.L. Pinos, et al., Effect of pterostilbene complexed with cyclodextrin on rat liver: potential reduction of oxidative damage and modulation of redox-sensitive proteins, Med. Chem. Res. 27 (2018) 2265-2278. https://doi.org/10.1007/s00044-018-2233-6.

[29] J. Jin, X. Wu, J. Yin, et al., Identification of genetic mutations in cancer: challenge and opportunity in the new era of targeted therapy, Front. Oncol. 9 (2019) 263. https://doi.org/10.3389/fonc.2019.00263.

[30] R. Nussinov, C.J. Tsai, H. Jang, et al., How can same-gene mutations promote both cancer and developmental disorders? Sci. Adv. 8 (2022) eabm2059. https://doi.org/10.1126/sciadv.abm2059.

[31] S.R. Jardim, L.M.P. de Souza, H.S.P. de Souza, et al., The rise of gastrointestinal cancers as a global phenomenon: unhealthy behavior or progress? Int. J. Environ. Res. Public Health 20 (2023) 3640. https://doi.org/10.3390/ijerph20043640.

[32] K.D. Miller, L. Nogueira, A.B. Mariotto, et al., Cancer treatment and survivorship statistics, 2019. CA Cancer J. Clin. 69 (2019) 363-385. https://doi.org/10.3322/caac.21565.

[33] H.J. Shin, J.M. Han, Y.S. Choi, et al., Pterostilbene suppresses both cancer cells and cancer stem-like cells in cervical cancer with superior bioavailability to resveratrol. Molecules 25 (2020) 228. https://doi.org/10.3390/molecules25010228.

[34] Z. Ma, X. Zhang, L. Xu, et al., Pterostilbene: mechanisms of its action as oncostatic agent in cell models and *in vivo* studies, Pharmacol. Res. 145 (2019) 104265. https://doi.org/10.1016/j.phrs.2019.104265.

[35] Y.R. Li, S. Li, C.C. Lin, et al., Effect of resveratrol and pterostilbene on aging and longevity, BioFactors 44 (2018) 69-82. https://doi.org/10.1002/biof.1400.

[36] J.H. Park, W.Y. Pyun, H.W. Park, et al., Cancer metabolism: phenotype, signaling and therapeutic targets, Cells 9 (2020) 2308. https://doi.org/10.3390/cells9102308.

[37] N. Jiang, Q. Dai, X. Su, et al., Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. Mol. Biol. Rep. 47 (2020) 4587-4629. https://doi.org/10.1007/s11033-020-05435-9.

[38] D. Gambini, E. Passoni, G. Nazzaro, et al., Basal cell carcinoma and hedgehog pathway inhibitors: focus on immune response, Front. Med. 9 (2022) 893063. https://doi.org/10.3389/fmed.2022.893063.

[39] M. Zhang, Y.Y. Zhang, Y. Chen, et al., TGF-β signaling and resistance to cancer therapy. Front. Cell Dev. Biol. 9 (2021) 786728. https://doi.org/10.3389/fcell.2021.786728.

[40] Z. Ma, Y. Yang, C. Fan, et al., Melatonin as a potential anticarcinogen for non-small-cell lung cancer. Oncotarget 7 (2016) 46768-46784. https://doi.org/10.18632/oncotarget.8776.

[41] Y.T. Chen, Z.Y. Huang, H.H. Tang, et al., Pterostilbene sensitizes cisplatin-resistant human bladder cancer cells with oncogenic HRAS, Cancers 12 (2020) 2869. https://doi.org/10.3390/cancers12102869.

[42] P. He, Y. Li, J. Hu, et al., Pterostilbene suppresses gastric cancer proliferation and metastasis by inhibiting oncogenic JAK2/STAT3 signaling: *in vitro* and *in vivo* therapeutic intervention, Phytomedicine 128 (2024) 155316. https://doi.org/10.1016/j.phymed.2023.155316.

[43] Y. Zhang, Y. Li, C. Sun, et al., Effect of pterostilbene, a natural derivative of resveratrol, in the treatment of colorectal cancer through Top1/Tdp1-mediated DNA repair pathway, Cancers 13 (2021) 4002. https://doi.org/10.3390/cancers13164002.

[44] Y. Feng, Y. Yang, C. Fan, et al., Pterostilbene inhibits the growth of human esophageal cancer cells by regulating endoplasmic reticulum stress, Int. J. Exp. Cell Physiol. Biochem. Pharmacol. 38 (2016) 1226-1244. https://doi.org/10.1159/000443071.

[45] Z. Li, J. Zhang, S. You, et al., Pterostilbene upregulates MICA/B *via* the PI3K/AKT signaling pathway to enhance the capability of natural killer cells to kill cervical cancer cells, Exp. Cell Res. 435 (2024) 113933. https://doi.org/10.1016/j.yexcr.2024.113933.

[46] J. Wawszczyk, K. Jesse, M. Kapral, Pterostilbene-mediated inhibition of cell proliferation and cell death induction in amelanotic and melanotic melanoma, Int. J. Mol. Sci. 24 (2023) 1115. https://doi.org/10.3390/ijms24021115.

[47] B. Xie, Z. Xu, L. Hu, et al., Pterostilbene inhibits human multiple myeloma cells *via* ERK1/2 and JNK pathway *in vitro* and *in vivo*, Int. J. Mol. Sci. 17 (2016) 1927. https://doi.org/10.3390/ijms17111927.

[48] Y. Kong, G. Chen, Z. Xu, et al., Pterostilbene induces apoptosis and cell cycle arrest in diffuse large B-cell lymphoma cells, Sci. Rep. 6 (2016) 37417. https://doi.org/10.1038/srep37417.

[49] S. Tungsukruthai, O. Reamtong, S. Roytrakul, et al., Targeting AKT/mTOR and Bcl-2 for autophagic and apoptosis cell death in lung cancer: novel activity of a polyphenol compound. Antioxidants 10 (2021) 534. https://doi.org/10.3390/antiox10040534.

[50] M. Mustafa, R. Ahmad, I.Q. Tantry, et al., Apoptosis: a comprehensive overview of signaling pathways, morphological changes, and physiological significance and therapeutic implications, Cells 13 (2024) 1838. https://doi.org/10.3390/cells13221838.

[51] M.A. Sayeed, M. Bracci, G. Lucarini, et al., Regulation of microRNA using promising dietary phytochemicals: possible preventive and treatment option of malignant mesothelioma, Biomed. Pharmacother. 94 (2017) 1197-1224. https://doi.org/10.1016/j.biopha.2017.07.075.

[52] V. Curti, A. Di Lorenzo, M. Dacrema, et al., *In vitro* polyphenol effects on apoptosis: an update of literature data, Semin. Cancer Biol. 46 (2017) 119-131. https://doi.org/10.1016/j.semcancer.2017.08.005.

[53] C.M. Hung, L.C. Liu, C.T. Ho, et al., Pterostilbene enhances TRAIL-induced apoptosis through the induction of death receptors and downregulation of cell survival proteins in TRAIL-resistant triple-negative breast cancer cells, J. Agric. Food Chem. 65 (2017) 11179-11191. https://doi.org/10.1021/acs.jafc.7b02358.

[54] I. Parkkinen, A. Their, M.Y. Asghar, et al., Pharmacological regulation of endoplasmic reticulum structure and calcium dynamics: importance for neurodegenerative diseases, Pharmacol. Rev. 75 (2023) 959-978. https://doi.org/10.1124/pharmrev.122.000701.

[55] M. González-Quiroz, H. Urra, C.M. Limia, et al., Homeostatic interplay between FoxO proteins and ER proteostasis in cancer and other diseases, Semin. Cancer Biol. 50 (2018) 42-52. https://doi.org/10.1016/j.semcancer.2018.01.011.

[56] Y. Nishiguch, R. Fujiwara-Tani, S. Nukaga, et al., Pterostilbene induces apoptosis from endoplasmic reticulum stress synergistically with anticancer drugs that deposit iron in mitochondria, Int. J. Mol. Sci. 25 (2024) 2611. https://doi.org/10.3390/ijms25052611.

[57] S.M. Soond, L.V. Savvateeva, V.A. Makarov, et al., Making connections: p53 and the cathepsin proteases as co-regulators of cancer and apoptosis, Cancers 12 (2020) 3476. https://doi.org/10.3390/cancers12113476.

[58] K. Engeland, Cell cycle regulation: p53-p21-RB signaling, Cell Death Differ. 29 (2022) 946-960. https://doi.org/10.1038/s41418-022-00988-z.

[59] A.M. Elsherbini, S.A. Sheweita, A.S. Sultan, Pterostilbene as a phytochemical compound induces signaling pathways involved in the apoptosis and death of mutant P53-breast cancer cell lines, Nutr. Cancer 73 (2021) 1976-1984. https://doi.org/10.1080/01635581.2020.1817513.

[60] Q. Jiang, L. Wang, X. Si, et al., Pterostilbene antagonizes homocysteine-induced oxidative stress, apoptosis and lipid deposition in vascular endothelial cells. Food Sci. Hum. Wellness 12 (2023) 1683-1692. https://doi.org/10.1016/j.fshw.2023.02.029.

[61] O. Surien, A.R. Ghazali, S.F. Masre, Chemopreventive effects of pterostilbene through p53 and cell cycle in mouse lung of squamous cell carcinoma model, Sci. Rep. 11 (2021) 14862. https://doi.org/10.1038/s41598-021-94508-7.

[62] S. Kawakami, M. Tsuma-Kaneko, M. Sawanobori, et al., Pterostilbene downregulates BCR/ABL and induces apoptosis of T315I-mutated BCR/ABL-positive leukemic cells, Sci. Rep. 12 (2022) 704. https://doi.org/10.1038/s41598-021-04654-1.

[63] F. Liu, X. Yang, M. Geng, et al., Targeting ERK, an Achilles' Heel of the MAPK pathway, in cancer therapy, Acta Pharm. Sin. B 8 (2018) 552-562. https://doi.org/10.1016/j.apsb.2018.01.008.

[64] H. Gao, Z. Liu, W. Xu, et al., Pterostilbene promotes mitochondrial apoptosis and inhibits proliferation in glioma cells, Sci. Rep. 11 (2021) 6381. https://doi.org/10.1038/s41598-021-85908-w.

[65] M.K. Ibrahim, S.R. Nandha, A.S. Patil, et al., Mitochondria-targeted derivative of pterostilbene, a dietary phytoestrogen, exhibits superior cancer cell cytotoxicity *via* mitochondrial superoxide mediated induction of autophagy, Adv. Redox Res. 8 (2023) 100071. https://doi.org/10.1016/j.arres.2023.100071.

[66] Q. Zeng, W. Lian, G. Wang, et al., Pterostilbene induces Nrf2/HO-1 and potentially regulates NF-κB and JNK-Akt/mTOR signaling in ischemic brain injury in neonatal rats, 3 Biotech 10 (2020) 1-16. https://doi.org/10.1007/s13205-020-02167-8.

[67] R.J. Chen, Y.J. Lyu, Y.Y. Chen, et al., Chloroquine potentiates the anticancer effect of pterostilbene on pancreatic cancer by inhibiting autophagy and downregulating the RAGE/STAT3 pathway, Molecules 26 (2021) 6741. https://doi.org/10.3390/molecules26216741.

[68] C. Musial, K. Siedlecka-Kroplewska, Z. Kmiec, et al., Modulation of autophagy in cancer cells by dietary polyphenols, Antioxidants 10 (2021) 123. https://doi.org/10.3390/antiox10010123.

[69] Y.J. Wang, Y.Y. Chen, C.M. Hsiao, et al., Induction of autophagy by pterostilbene contributes to the prevention of renal fibrosis *via* attenuating NLRP3 inflammasome activation and epithelial-mesenchymal transition, Front. Cell Dev. Biol. 8 (2020) 436. https://doi.org/10.3389/fcell.2020.00436.

[70] J.L. He, X.H. Dong, Z.H. Li, et al., Pterostilbene inhibits reactive oxygen species production and apoptosis in primary spinal cord neurons by activating autophagy *via* the mechanistic target of rapamycin signaling pathway, Mol. Med. Rep. 17 (2018) 4406-4414. https://doi.org/10.3892/mmr.2018.8412.

[71] W.S. Lin, J.V. Leland, C.T. Ho, et al., Occurrence, bioavailability, anti-inflammatory, and anticancer effects of pterostilbene, J. Agric. Food Chem. 68 (2020) 12788-12799. https://doi.org/10.1021/acs.jafc.9b07860.

[72] C.L. Yu, S.F. Yang, T.W. Hung, et al., Inhibition of eIF2α dephosphorylation accelerates pterostilbene-induced cell death in human hepatocellular carcinoma cells in an ER stress and autophagy-dependent manner, Cell Death Dis. 10 (2019) 418. https://doi.org/10.1038/s41419-019-1639-5.

[73] C.J. Huang, P.C. Shieh, J.S. Yang, et al., Pterostilbene suppressed cell viability, induced apoptosis and autophagy of cisplatin-resistant gastric cancer cells, Anticancer Res. 45 (2025) 511-523. https://doi.org/10.21873/anticanres.17440.

[74] P. Liu, W. Tang, K. Xiang, et al., Pterostilbene in the treatment of inflammatory and oncological diseases, Front. Pharmacol. 14 (2024) 1323377. https://doi.org/10.3389/fphar.2023.1323377.

[75] C.J. Sherr, J. Bartek, Cell cycle–targeted cancer therapies, Annu. Rev. Cancer Biol. 1 (2017) 41-57. https://doi.org/10.1146/annurev-cancerbio-040716-075628.

[76] K.T. Tan, P.W. Chen, S. Li, et al., Pterostilbene inhibits lung squamous cell carcinoma growth *in vitro* and *in vivo* by inducing S phase arrest and apoptosis, Oncol. Lett. 18 (2019) 1631-1640. https://doi.org/10.3892/ol.2019.10499.

[77] G.L. Russo, E. Stampone, C. Cervellera, et al., Regulation of p27Kip1 and p57Kip2 functions by natural polyphenols, Biomolecules 10 (2020) 1316. https://doi.org/10.3390/biom10091316.

[78] S. Dhar, A. Kumar, A.M. Rimando, et al., Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer, Oncotarget 6 (2015) 27214-27226. https://doi.org/10.18632/oncotarget.4877.

[79] D. Yu, Y. Zhang, G. Chen, et al., Targeting the PI3K/Akt/mTOR signaling pathway by pterostilbene attenuates mantle cell lymphoma progression, Acta Biochim. Biophys. Sin. 50 (2018) 782-792. https://doi.org/10.1093/abbs/gmy070.

[80] H. Lee, Y. Kim, J.H. Jeong, et al., ATM/CHK/p53 pathway dependent chemopreventive and therapeutic activity on lung cancer by pterostilbene, PLoS One 11 (2016) e0162335. https://doi.org/10.1371/journal.pone.0162335.

[81] M.J. Sanaei, A. Baghery Saghchy Khorasani, A. Pourbagheri-Sigaroodi, et al., The PI3K/Akt/mTOR axis in colorectal cancer: oncogenic alterations, non-coding RNAs, therapeutic opportunities, and the emerging role of nanoparticles, J. Cell. Physiol. 237 (2022) 1720-1752. https://doi.org/10.1002/jcp.30655.

[82] N.A. Butt, A. Kumar, S. Dhar, et al., Targeting MTA1/HIF-1α signaling by pterostilbene in combination with histone deacetylase inhibitor attenuates prostate cancer progression, Cancer Med. 6 (2017) 2673-2685. https://doi.org/10.1002/cam4.1209.

[83] F. Xing, Y. Liu, S. Sharma, et al., Activation of the c-Met pathway mobilizes an inflammatory network in the brain microenvironment to promote brain metastasis of breast cancer, Cancer Res. 76 (2016) 4970-4980. https://doi.org/10.1158/0008-5472.CAN-15-3541.

[84] V. Tambe, R. Pujari, A. Karnik, et al., Pterostilbene: a review on its pharmacological activities, Res. J. Pharm. Technol. 16 (2023) 5514-5521. https://doi.org/10.52711/0974-360X.2023.00892.

[85] C.W. Lin, Y.E. Chou, H.L. Chiou, et al., Pterostilbene suppresses oral cancer cell invasion by inhibiting MMP-2 expression, Expert Opin. Ther. Targets 18 (2014) 1109-1120. https://doi.org/10.1517/14728222.2014.947962.

[86] Y. Huang, J. Du, Y. Mi, et al., Long non-coding RNAs contribute to the inhibition of proliferation and EMT by pterostilbene in human breast cancer, Front. Oncol. 8 (2018) 629. https://doi.org/10.3389/fonc.2018.00629.

[87] S. Dhar, A. Kumar, L. Zhang, et al., Dietary pterostilbene is a novel MTA1-targeted chemopreventive and therapeutic agent in prostate cancer, Oncotarget 7 (2016) 18469-18484. https://doi.org/10.18632/oncotarget.7841.

[88] R. Carrano, M. Grande, E. Leti Maggio, et al., Dietary polyphenols effects on focal adhesion plaques and metalloproteinases in cancer invasiveness, Biomedicines 12 (2024) 482. https://doi.org/10.3390/biomedicines12030482.

[89] H.I. Kutbi, A.K. Kammoun, D. Farag El-Telbany, Amelioration of pterostilbene antiproliferative, proapoptotic, and oxidant potentials in human breast cancer MCF7 cells using zein nanocomposites, Int. J. Nanomed. (2021) 3059-3071. https://doi.org/10.2147/IJN.S303975.

[90] T. Pan, L. Peng, J. Dong, L. Li. Pterostilbene induces pyroptosis in breast cancer cells through pyruvate kinase 2/Caspase-8/gasdermin C signaling pathway, Int. J. Mol. Sci. 25 (2024) 10509. https://doi.org/10.3390/ijms251910509.

[91] R. Wakimoto, M. Ono, M. Takeshima, et al., Differential anticancer activity of pterostilbene against three subtypes of human breast cancer cells, Anticancer Res. 37 (2017) 6153-6159. https://doi.org/10.21873/anticanres.12064.

[92] K. Ma, H. Chen, K. Wang, et al., Pterostilbene inhibits the metastasis of TNBC *via* suppression of *β*-catenin-mediated epithelial to mesenchymal transition and stemness, J. Funct. Foods 96 (2022) 105219. https://doi.org/10.1016/j.jff.2022.105219.

[93] K.W. Tam, C.T. Ho, S.H. Tu, et al., *α*-Tocopherol succinate enhances pterostilbene anti-tumor activity in human breast cancer cells *in vivo* and *in vitro,* Oncotarget 9 (2017) 4593-4606. https://doi.org/10.18632/oncotarget.23390.

[94] H. Xue, M. Li. Protective effect of pterostilbene on sepsis-induced acute lung injury in a rat model *via* the JAK2/STAT3 pathway, Ann. Transl. Med. 8 (2020) 1452. https://doi.org/10.21037/atm-20-5814.

[95] Y. Zhang, Z. Han, A. Jiang, et al., Protective effects of pterostilbene on lipopolysaccharide-induced acute lung injury in mice by inhibiting NF-κB and activating Nrf2/HO-1 signaling pathways, Front. Pharmacol. 11 (2021) 591836. https://doi.org/10.3389/fphar.2020.591836.

[96] Y.H. Hsiao, N.C. Chen, Y.C. Koh, et al., Pterostilbene inhibits adipocyte conditioned-medium-induced colorectal cancer cell migration through targeting FABP5-related signaling pathway, J. Agric. Food Chem. 67 (2019) 10321-10329. https://doi.org/10.1021/acs.jafc.9b03997.

[97] J. Wawszczyk, K. Jesse, S. Smolik, et al., Mechanism of pterostilbene-induced cell death in HT-29 colon cancer cells, Molecules 27 (2022) 369. https://doi.org/10.3390/molecules27020369.

[98] W. Wen, G. Lowe, C.M. Roberts, et al., Pterostilbene suppresses ovarian cancer growth *via* induction of apoptosis and blockade of cell cycle

progression involving inhibition of the STAT3 pathway. Int. J. Mol. Sci. 19 (2018) 1983. https://doi.org/10.3390/ijms19071983.

[99] S. De, S. Paul, A. Manna, et al., Phenolic phytochemicals for prevention and treatment of colorectal cancer: a critical evaluation of *in vivo* studies. Cancers 15 (2023) 993. https://doi.org/10.3390/cancers15030993.

[100] R. Fernandes, C. Costa, R. Fernandes, et al., Inflammation in prostate cancer: exploring the promising role of phenolic compounds as an innovative therapeutic approach, Biomedicines 11 (2023) 3140. https://doi.org/10.3390/biomedicines11123140.

[101] S. Mirzaei, M.D.A. Paskeh, Y. Saghari, et al., Transforming growth factor-beta (TGF-β) in prostate cancer: a dual function mediator? Int. J. Biol. Macromol. 206 (2022) 435-452. https://doi.org/10.1016/j.ijbiomac.2022.02.094.

[102] T. Mengie Ayele, Z. Tilahun Muche, A. Behaile Teklemariam, et al., Role of JAK2/STAT3 signaling pathway in the tumorigenesis, chemotherapy resistance, and treatment of solid tumors: a systemic review, J. Inflamm. Res. 15 (2022) 1349-1364. https://doi.org/10.2147/JIR.S353489.

[103] M. Prasad, S. Tamil Selvan, R. Shanmugam, Influence of pterostilbene on gene expression in liver cancer: an *in silico* analysis, Cureus 16 (2024) e53098. https://doi.org/10.7759/cureus.53098.

[104] M. Cao, L. Bai, H. Wei, et al., Dietary supplementation with pterostilbene activates the PI3K-AKT-mTOR signalling pathway to alleviate progressive oxidative stress and promote placental nutrient transport, J. Anim. Sci. Biotechnol. 15 (2024) 133. https://doi.org/10.1186/s40104-024-01090-9.

[105] Y. Wang, Z. Wang, S. Li, et al., Deciphering JAK/STAT signaling pathway: a multifaceted approach to tumorigenesis, progression and therapeutic interventions. Int. Immunopharmacol. 131 (2024) 111846. https://doi.org/10.1016/j.intimp.2024.111846.

[106] T. Chen, X. Zhang, G. Zhu, et al., Quercetin inhibits TNF-α induced HUVECs apoptosis and inflammation *via* downregulating NF-kB and AP-1 signaling pathway *in vitro,* Medicine 99 (2020) e22241. https://doi.org/10.1097/MD.0000000000022241.

[107] X.P. Wang, W.P. Xie, Y.F. Bi, et al., Quercetin suppresses apoptosis of chondrocytes induced by IL-1β *via* inactivation of p38 MAPK signaling pathway, Exp. Ther. Med. 21 (2021) 468. https://doi.org/10.3892/etm.2021.9899.

[108] Z. Lu, H. Wang, M. Ishfaq, et al., Quercetin and AMPK: a dynamic duo in alleviating MG-induced inflammation *via* the AMPK/SIRT1/NF-κB pathway, Molecules 28 (2023) 7388. https://doi.org/10.3390/molecules28217388.

[109] K. Mohankumar, A.P. Francis, S. Pajaniradje, et al., Synthetic curcumin analog: inhibiting the invasion, angiogenesis, and metastasis in human laryngeal carcinoma cells *via* NF-kB pathway, Mol. Biol. Rep. 48 (2021) 6065-6074. https://doi.org/10.1007/s11033-021-06610-8.

[110] A.Q. Khan, E.I. Ahmed, N. Elareeret al., Curcumin-mediated apoptotic cell death in papillary thyroid cancer and cancer stem-like cells through targeting of the JAK/STAT3 signaling pathway, Int. J. Mol. Sci. 21 (2020) 438. https://doi.org/10.3390/ijms21020438.

[111] Z. Cheng, Z. Zhang, Y. Han, et al., A review on anti-cancer effect of green tea catechins, J. Funct. Foods 74 (2020) 104172. https://doi.org/10.1016/j.jff.2020.104172.

[112] M. Alavi, T. Farkhondeh, M. Aschner, et al., Resveratrol mediates its anticancer effects by Nrf2 signaling pathway activation, Cancer Cell Int. 21 (2021) 579. https://doi.org/10.1186/s12935-021-02280-5.

[113] H. Naeem, U. Momal, M. Imran, et al., Anticancer perspectives of genistein: a comprehensive review, Int. J. Food Prop. 26 (2023) 3305-3341. https://doi.org/10.1080/10942912.2023.2281257.

[114] A.A. Hasan, V. Tatarskiy, E. Kalinina, Synthetic pathways and the therapeutic potential of quercetin and curcumin, Int. J. Mol. Sci. 23 (2022) 14413. https://doi.org/10.3390/ijms232214413.

[115] W.H. Talib, A.R. Alsayed, M. Barakat, et al., Targeting drug chemoresistance in cancer using natural products, Biomedicines 9 (2021) 1353. https://doi.org/10.3390/biomedicines9101353.

[116] Y.H. Hsu, S.Y. Chen, S.Y. Wang, et al., Pterostilbene enhances cytotoxicity and chemosensitivity in human pancreatic cancer cells, Biomolecules 10 (2020) 709. https://doi.org/10.3390/biom10050709.

[117] F. Busato, B.E. Khouzai, M. Mognato. Biological mechanisms to reduce radioresistance and increase the efficacy of radiotherapy: state of the art, Int. J. Mol. Sci. 23 (2022) 10211. https://doi.org/10.3390/ijms231810211.

[118] E.M. Moustafa, E.R. Rashed, R.R. Rashed, Pterostilbene inhibits dyslipidemia-induced activation of progenitor adipose gene under high-fat diet and radiation stressor, Nat. Prod. Commun. 16 (2021) 1934578X211001267. https://doi.org/10.1177/1934578X211001267.

[119] Y. Li, C. Sun, Y. Zhang, et al., Phase I metabolism of pterostilbene, a dietary resveratrol derivative: metabolite identification, species differences, isozyme contribution, and further bioactivation, J. Agric. Food Chem. 71 (2023) 331-346. https://doi.org/10.1021/acs.jafc.2c05334.

[120] X. Wang, K. Mao, X. Zhang, et al., Red blood cell derived nanocarrier drug delivery system: a promising strategy for tumor therapy, Interdiscip. Med. 2 (2024) e20240014. https://doi.org/10.1002/INMD.20240014.

[121] W. Wang, K. Li, D. Bai, et al., Pterostilbene: a potential therapeutic agent for fibrotic diseases, Inflammopharmacology 32 (2024) 975-989. https://doi.org/10.1007/s10787-024-01440-z.

[122] Y. Zou, X. Wang, D. Bi, et al., Pterostilbene nanoparticles with small particle size show excellent anti-breast cancer activity *in vitro* and *in vivo,* Nanotechnology 32 (2021). https://doi.org/10.1088/1361-6528/abfdec.

[123] N.A. Hanafy, R.H. Abdelbadea, A.E. Abdelaziz, et al., Formulation and optimization of folate-bovine serum albumin-coated ethoniosomes of pterostilbene as a targeted drug delivery system for lung cancer: *in vitro* and *in vivo* demonstrations, Cancer Nanotechnol. 14 (2023) 49. https://doi.org/10.1186/s12645-023-00197-4.

[124] S.A.A. Gaber, M. Nasr, M.A. Hamzawy. Pterostilbene lipid nanocapsules as a promising system for treatment of hepatocellular carcinoma: formulation, characterization, and cellular/*in vivo* appraisal, J. Drug Deliv. Sci. Technol. 92 (2024) 105310. https://doi.org/10.1016/j.jddst.2023.105310.

[125] P.S. Phansalkar, Z. Zhang, S. Verenich, et al., in Pharmacokinetics and bioavailability enhancement of natural products, Cham: Springer International Publishing. Switzerland, 2020, pp: 109-141. https://doi.org/10.1007/978-3-030-39855-2_4.

[126] A. Gu, J. Li, M.Y. Li, et al., Patient-derived xenograft model in cancer: establishment and applications, MedComm. 6 (2025) e70059. https://doi.org/10.1002/mco2.70059.