Pharmacological Research 145 (2019) 104265

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Pterostilbene: Mechanisms of its action as oncostatic agent in cell models and *in vivo* studies

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ARTICLE INFO

Keywords:
Pterostilbene
Cancer
Oncostatic effects
Drug synergy
Cancer hallmarks

ABSTRACT

Pterostilbene, a natural dimethylated analog of resveratrol, exerts pleiotropic anticancer effects against a variety of cancer types. Due to the better lipophilic and oral absorption, higher cellular uptake and a longer half-life than resveratrol, pterostilbene may have a good prospect in the future clinic application. In this review, we summarize the previous in vitro and in *vivo* studies about the anticancer actions of pterostilbene on malignances, and we also evaluate the evidence related to the effects of pterostilbene on blocking normal cell carcinogenesis. Special focus is placed on the oncostatic effects of pterostilbene, including inhibition of tumor growth, metastasis, angiogenesis and cancer stem cells, activation of apoptosis, and enhancement of immunotherapy. We then clarify the emerging investigations about pterostilbene and chemotherapy and radiotherapy. Taken together, the information complied herein may serve as a comprehensive reference for the anticancer mechanisms of pterostilbene and may advance it as a future adjuvant therapeutic agent for cancer.

1. Introduction

Cancer is the second leading cause of death and remains a deadly disease [1,2]. Chemoradiotherapy, one of the primary cancer therapies, often leads to adverse side effects on normal cells or tissues, thus limiting their application as an oncotherapy [3,4]. The poor prognosis and worse overall survival of cancer spotlights the urgent need for novel therapeutic strategies regarding the cancer prevention and treatment [5]. This has spurred us to find new agents peculiarly from natural materials with few undesirable side effects in cancer therapy. Pterostilbene is a potential anticarcinogen lack of toxic and harmful side effects and has attracted more attention [6,7].

Pterostilbene (3,5-dimethoxy-4′-hydroxystilbene) is a natural dimethylated analog of the resveratrol (3,5,4′-trihydroxystilbene) found mainly in blueberries and grapes [8,9]. Pterostilbene is similar to resveratrol in pharmacology such as anticancer, hypolipidemic activity, anti-diabetes and beneficial effects on the CNS and cardiovascular diseases, which the mechanisms of are related to the effects of antioxidant and anti-inflammation [8,10–13]; however, pterostilbene's antioxidant and anticancer effects are more potent [8]. Due to the twomethoxy groups, pterostilbene exhibits better bioavailability, leading to rise in oral and lipophilic absorption, and a longer half-life than resveratrol [14,15]. Moreover, pterostilbene could prohibit the growth of a lot of cancers: breast [16–20], lung [6,21–23], prostate [24–27], melanoma [28–30], colon [31,32], etc (Table 1). The oncostatic mechanisms of pterostilbene correlate with several hallmarks of cancer, including anti-proliferation [25,31,33,34], induction of apoptosis [6,32–36], inhibition of invasion and metastasis [17,24,30,37], anti-angiogenesis [16,27,38], enhancement of immunotherapy [39,40] and inhibition of cancer stem cell [22,41,42]. Consequently, these findings confirm that pterostilbene is a potential anticarcinogen and offer an incentive for further work in this field.

In this review, we systematically introduce the emerging anticancer actions of pterostilbene. We first briefly discuss the anticarcinogenic roles of pterostilbene against cancer. We then describe the anticancer actions of pterostilbene in-depth. Subsequently, we depict the

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https://doi.org/10.1016/j.phrs.2019.104265
Received 8 February 2019; Received in revised form 23 April 2019; Accepted 5 May 2019
Available online 09 May 2019
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Table 1
Oncostatic effects of pterostilbene on various cancers.

Cancer type	Models	Pterostilbene treatment	Effects	Underlying mechanisms	References
Breast cancer	MDA-231 and ZR-751 cells	25, 50, 75 μM for 24 h in culture	Anti- proliferation	Inhibition of JAK/STAT3 activation	[71]
	MCF-7 cells	40-80 μM in culture	Inducing apoptosis Anti-invasion and metastasis	Up-regulation of ROS generation, caspase-3, Bax;Down-regulation of Bcl-2, MMP-9, AMACR	[26]
	MCF-7 and MDA-MB-231 cells	10-100 μM in culture	Inducing apoptosis	Up-regulation of caspase-3/7, superoxide anion, mitochondrial depolarization	[78]
	BT-20 and MDA-MB-468 cells	0, 10, 20, 40, 80 μM for 12, 24, 48 h in culture	Inducing apoptosis	Up-regulation of DR4 and DR5; Activation of the ROS/ERS/ERK1/2 and p38/CHOP signaling pathways; Down-regulation of antiapoptotic Bcl-2 family members	[79]
	MCF-7 and MDA-MB-231 cells	2.5, 5, 10 μM for 48 h in culture	Anti-invasion and metastasis Inhibition of CSC	Up-regulation of miR-448; Down-regulation of NF-κB expression and EMT	[18]
	MDA-MB-231 cells	10, 25, 50 μM for 24 h in culture	Anti-invasion and metastasis	Inhibition of invadopodium formation and MMP-2/9	[19]
	MCF-7 cells	5, 25 μM for 4, 8, 24 h in culture	Inhibition of CSC	Inhibition of hedgehog/Akt/GSK-3β signaling	[110]
	MDA-MB-231-luc-D3H2LN cells	25, 50 μM for 48 h in culture	Inhibition of CSC	Up-regulation of miR-143, miR-200c and Ago2 expression	[20]
	MDA-MB-231 and Hs578 t cells; MDA-MB-231-bearing NOD/SCID mice	10 μM for 6, 12, 24 h in culture; 10 mg/kg·bw/3 times a week for 3 weeks/intraperitoneally administered	Anti-invasion and metastasis	Up-regulation of miR-205; Inhibition of EMT and Src/Fak signaling	[17]
	231BrM and SKBrM3 cells; nude mice	10, 30 μM in culture; 30 mg/kg/ every two days/ intraperitoneal injection	Anti-invasion and metastasis Anti-angiogenesis	Inhibition of c-Met pathway	[16]
Lung cancer	Lewis lung carcinoma cells	25, 50, 100 μM for 4 h in culture	Anti-invasion and metastasis	Inhibition of Akt/ERK-regulated polyFN assembly	[21]
	A549 and H441 cells	5, 10, 20 μM in culture	Inhibiting CSC	Down-regulation of MUC1, NF-κB, β-catenin, Sox2, and CD133	[22]
	A549 cells	2.5, 5, 10 μM in culture	Anti- proliferation	Activation of ATM/CHK/p53 pathway	[69]
	NCI-H460 and SK-MES-1 cells	10-100 μM for 24, 48, 72 h in culture	Inducing apoptosis	Up-regulation of caspase 3/7	[76]
	PC9 and A549 cells; PC9 cell xenograft nude mice	20, 40, 60 μM for 24, 48 h in culture; 5 0 mg/kg/ every day for 28 days/administered intraperitoneally	Inducing apoptosis	Activation of ERS	[6]
	Male A/J mice treated with urethane	50, 250 mg/kg/5 times a week, 25 weeks/ intraperitoneal injection	Anti- proliferation	Down-regulation of EGFR, Akt/mTOR and ERK1/2 pathways	[23]
Prostate cancer	PC3 cells	40-80 μM in culture	Inducing apoptosis Anti-invasion and metastasis	Up-regulation of ROS generation, caspase-3, Bax; Down-regulation of Bcl-2, MMP-9, AMACR	[26]
	DU145 and 22Rv1 cells; DU145 cell xenograft nude mice	50 μM in culture; 50 mg/kg/daily, 39 days/ intraperitoneal injection	Anti-proliferation	Down-regulation of miR-17, miR-21a and miR-106a/b	[25]
	LNCaP and PC3M cells; prostate-specific Pten-null mice	50 μM for 24 h in culture; 10 mg/kg·bw/5 days a week, for 10 weeks /intraperitoneal injection	Anti-invasion and metastasis Anti-angiogenesis	Inhibition of MTA1/HIF-1α signaling	[27]
	Prostate specific Pten heterozygous and Pten knockout mice	100 mg/kg/8-10 months/diet or 10 mg/kg·bw/ daily intraperitoneal injection	Anti-invasion and metastasis Anti-angiogenesis	Inhibition of MTA1	[24]
Melanoma	human melanoma SK-MEL-2 and MeWo cells	25, 50, 75 μM for 24, 48, 72 h in culture	Inducing apoptosis	Up-regulation of caspase-3/7 activity	[28]
	malignant B16 melanoma F10 cells	40 μM for 60 min in culture	Anti-invasion and metastasis	Down-regulation of VCAM-1, Bcl-2 and iNOS gene expression; Up-regulation of eNOS expression	[29]
	malignant B16 melanoma F10 cells	40 μM for 60 min in culture	Anti-invasion and metastasis Inducing apoptosis	Down-regulation of VCAM-1 and Bcl-2; Up-regulation of Bax	[30]
Colon cancer	HT-29 cells; azoxymethane-injected F344 male rats	50 μM for 30 min, 4 h or 30 μM for 1, 2 h in culture; 40 p.p.m./45 weeks/diet	Anti- proliferation	Down-regulation of PCNA, β-catenin, cyclin D1 and c-MYC	[31]
	azoxymethane-treated male ICR mice	50, 250 p.p.m./6, 23 weeks/diet	Inducing apoptosis Anti-angiogenesis	Up-regulation of Bax, Fas, FasL; activating caspase-8 and truncating Bid; Down-regulation of VEGF	[32]
Oral squamous cell carcinoma	SAS and OECM-1 cells	0-40 μM for 24 h in culture	Anti- proliferation Inducing apoptosis	Induction of G0/G1 and S phase arrest; Up-regulation of cleaved caspase-3/8/9	[83]
	SCC-9 cells	0-20 μM for 24 h in culture	Anti-invasion and metastasis	Inhibition of Akt, ERK1/2 and JNK1/2 phosphorylation and MMP-2 and u-PA expression	[96]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Models	Pterostilbene treatment	Effects	Underlying mechanisms	References
Pancreas cancer	MIA PaCa-2 and PANC-1 cells	20-100 μM for 24, 48, 72 h in culture	Anti- proliferation Inducing apoptosis	Induction of G0/G1 and S phase arrest; Up-regulation of caspase-3/7 activity; Down-regulation of mitochondrial membrane potential	[82]
	MIA PaCa-2 and PANC-1 cells	25, 50, 75 μM for 24, 48 h in culture	Inducing apoptosis	Up-regulation of Cytosolic Cytochrome C and Smac/DIABLO, MnSOD activity; Down-regulation of oxidative stress and p-STAT3	[81]
Glioblastoma multiforme	GBM8401 cell	2, 4 μM in culture	Inhibition of CSC	Up-regulation of miR-205; Down-regulation of GRP78, c-Myc, β-catenin and vimentin	[42]
Gastric carcinoma	CCRC 60102 cell	80 μM for 24 h in culture	Anti- proliferation Inducing apoptosis	Induction of G0/G1 arrest; Up-regulation of mitochondrial dysfunction, ROS production, and release of cytochrome c, caspase-2/3/8/9 activity, Fas and FasL expression, Bad, Bax and Bid	[33]
lymphoma	SUDHL-4, DB, NU-DUL-1, TMD8 cells	20-120 μM for 24, 48, 72 h in culture	Anti- proliferation Inducing apoptosis Anti-invasion and metastasis	Induction of S-phase arrest; Up-regulation of caspase-3/8/9 activity, ROS generation, Bax; Down-regulation of Bcl-2 and mitochondrial membrane potential; Suppression of ERK1/2 and activation of p38MAPK signaling pathways	[34]
Myeloma	H929 Cells	10, 20, 30, 40, 50 μM for 24, 48, 72 h in culture	Anti- proliferationInducing apoptosis	Induction of G0/G1 arrest; Up-regulation of cleaved caspase-3/8/9, ROS generation and activation of ERK1/2 and JNK pathway; Down-regulation of mitochondrial membrane potential	[9]
Bladder cancer	T24 and T24R cells	50, 75, 100 μM for 24, 48, 72 h in culture	Anti- proliferation Inducing apoptosis	Induction of G0/G1 arrest; Up-regulation of caspase-3 activity; Down-regulation of Bcl-2, Bcl-xl	[75]
Hepatocellular carcinoma	HepG2 cells	10, 25, 50 μM for 24 h in culture	Anti-invasion and metastasis	Down-regulation of PKC, EGF, VEGF and MMP-9; Inhibition of MAPK/AP-1 and PI3K/Akt/NF-κB	[37]
Cervical cancer	HeLa Cells	80 μM for 48 h in culture	Inducing apoptosis	Activation of ERS and Nrf2/ARE pathway	[84]
Esophageal cancer	EC109 and TE1 cells; EC109 cell xenograft nude mice	5, 10, 15, 50, 100, 150 μM for 24 h in culture; 100, 200 mg/kg/5 times a week for 20 days/ administered intraperitoneally	Inducing apoptosis Anti-invasion and metastasis	Activation of ERS; ROS-dependent suppression of Sp-1	[36]

Abbreviations: Ago2, Argonaute 2; Akt, protein kinase B; AMACR, a-methylacyl-CoA; AP-1, activator protein-1; ARE, antioxidant response element; ATM, ataxia telangiectasia mutated; Bad, bcl-Associated Death Protein; Bax, Bcl-2 associated X protein; Bcl-xl, bcl-X Protein; Bcl-2, B-cell lymphoma-2; Bid, BH3 interacting domain death agonist protein; CHK, checkpoint kinase; CHOP, C/EBP homologous protein; c-Met, mesenchymal-epithelial transition factor; CSC, cancer stem cell; DR4/5, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors 1/2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; eNOS, endothelial nitric-oxide synthetase; ERK1/2, extracellular signal regulated kinases 1/2; ERS, endoplasmic reticulum stress; Fak, focal adhesion kinase; Fas, factor associated suicide; FasL, factor associated suicide ligand; GSK-3β: glycogen synthase kinase-3; GRP78, glucose regulated protein 78; HIF-1α, hypoxic response transcription factor-1α; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; JNK1/2: c-Jun N-terminal kinase 1/2; MMP-2, matrix metalloprotein-2; MnSOD, manganese superoxide dismutase; MTA1, metastasis-associated protein 1; mTOR, mammalian target of rapamycin; Muc1, mucin 1; NF-κB, nuclear factor kappa B; Nrf2, NF-E2-related factor 2; PCNA, proliferating-cell nuclear antigen; PI3K, phosphoinositide 3 kinase; PKC, protein kinase C; polyFN, polymeric fibronectin; ROS, reactive oxygen species; Smac/DIABLO, second mitochondria-derived activator of caspase/ direct IAP-binding protein with low pI; Sox2, sex-determining region Y HMG-box 2; Src, steroid receptor coactivator; STAT3: signal transducer and activator of transcription 3; Sp-1, specificity protein 1; VCAM-1, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor; u-PA, urokinase-type plasminogen activator.

connection between pterostilbene and chemotherapy, radiotherapy respectively. Ultimately, we extend our attention to several novel potential directions and further perspectives in this research area.

2. Anti-inflammatory role of pterostilbene on carcinogenesis

2.1. In vitro studies

Inflammation is well-known causally correlated with carcinogenesis, due to acting as a driving force during the transformation of premalignancy to malignancy [43–46]. The aberrant secretion and expression of inflammatory factors are critical for tumorigenesis [47,48]. Pterostilbene was found to significantly downregulate the cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) levels [32,49–54], which are involved in inflammatory process [49]. It was found pterostilbene blocked the NF-κB signaling through inhibiting its nuclear translocation, thus suppressing the pro-inflammatory cytokines (e.g., TNFα, IL-1β, IL-6 and IL-18) expression, and inhibiting NO production in vitro [49,51,55–58]. In addition, pterostilbene suppressed the iNOS and COX-2 gene expression in LPS-stimulated macrophages through repressing NF-κB activation by MAPK and PI3K/Akt cascades depression [51,54].

2.2. In vivo studies

In female Balb/c mouse epidermis treated with tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) [53], pterostilbene markedly suppressed the NF-κB activity via inhibiting the p65 nucleus translocation and preserving the IκBα cytosol retention. Additionally, pterostilbene also inhibited the AP-1 activity via reducing the c-Jun binding to TPA-responsive element (TRE) site [53]. Therefore, the reduced AP-1 and NF-κB transcription factors activation decreased the expression and activity of COX-2 and iNOS [53]. Furthermore, pterostilbene suppressed LPS-induced NF-κB translocation by repressing the MAPK (ERK1/2 and p38) and PI3K/Akt pathway, subsequently downregulating the iNOS and COX-2 expression in TPA-treated mouse skin [50] and in λ-carrageenan-induced rat paw edema model [54] (Fig. 1).

3. Antioxidative role of pterostilbene on carcinogenesis

3.1. In vitro studies

Continuous oxidative stress is now considered to be correlated with neoplasm occurrence and tumor progression [59]. Oxidative stress can cause DNA damage and gene mutations, resulting in carcinogenesis and finally causing cancer [47] (Fig. 1); thus inhibition of oxidative stress is a potentially important protective means to reduce carcinogenesis [60].

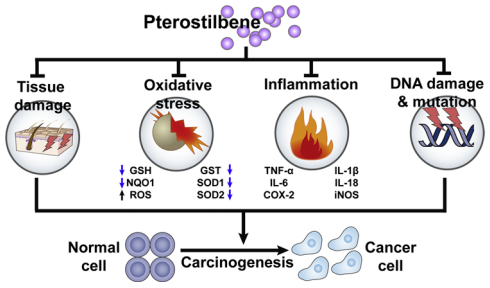

Fig. 1. Effect of pterostilbene on the prevention of carcinogenesis. Pterostilbene attenuates tissue damage, oxidative stress, inflammation, and DNA damage and mutation. Therefore, pterostilbene inhibits normal cell carcinogenesis induced by these factors. Abbreviations: COX-2, cyclooxygenase-2; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; GSH, glutathione; GST, glutathione S-transferase; NQO1, NAD(P)H quinone oxidoreductase; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; TNF-α, tumor necrosis factor-α.

Harun et al. reported pterostilbene could significantly increase the glutathione S-transferase (GST) activity and its thiol conjugate, glutathione (GSH) level as well as NAD(P)H quinone oxidoreductase (NQO1) activity in colon HT-29 cells [61]. Therefore, pterostilbene is able to protect to the cells from the reactive species induced by injury [61]. Studies have reported that pterostilbene increased the expression and activity of superoxide dismutase 1 and 2 (SOD1 and SOD2) by inhibiting miR-377, thus reducing oxidation in fructose-induced conditionally immortalized mouse podocyte [62,63]. Furthermore, pterostilbene effectively activated NF-E2-related factor 2/antioxidant response element (Nrf2/ARE) via PI3K/Akt signaling, and subsequently increased endogenous defense, scavenged UVB-induced ROS generation, and enhanced the ability of DNA recovery, thereby protecting against UVB-related photo-injury in UVB-irradiated immortalized human keratinocytes (HaCaT) cells [64]. It's well known Nrf2/ARE pathway is recognized as the central defense mechanism against oxidative stress, regulating the expression of a battery of detoxifying/antioxidant genes [64,65]. Kelch-like ECH-associated protein 1 (Keap1) is a scaffolding protein for proteasome degradation and the repressor of Nrf2 [64]. When disrupting from Keap1, Nrf2 rapidly undergoes nuclear translocation, and transactivates the ARE in the promoter region of target genes (e.g., catalase, SOD, GPx, HO-1, NQO1, and γ-glutamate-cysteine ligase) [64,66].

3.2. In vivo studies

Except above mentioned in vitro studies, suppressing miR-377 to up-regulate SOD was confirmed in pterostilbene-treated fructose-fed Sprague Dawley rats [62,63]. Interestingly, pterostilbene has been found to effectively prevent ultraviolet B (UVB) (180 mJ/cm^2, 3 doses/week for 6 months)-induced acute skin damage and carcinogenesis in SKH-1 hairless mice [66]. Pterostilbene exerted the protective effect via inhibiting Keap1 thus activating Nrf2/ARE pathway [66]. (Fig. 1). Taken together, these evidences demonstrate that pterostilbene should be regarded as a valuable drug for inhibition of carcinogenesis.

4. Effect of pterostilbene on cancer cell proliferation and cell cycle arrest

4.1. In vitro studies

Arguably the most fundamental trait of cancer cells involves their ability to sustain chronic proliferation [67]. Studies have revealed that pterostilbene inhibited proliferation of a wide range of tumor cells, including gastro [33], lung [23,68,69], lymphoma [34], colon [31], prostate [25,68], breast [70,71] cancer cells. Since aberrant activity of various cell cycle proteins results in uncontrolled cancer cell proliferation, cell cycle regulators are regarded as attractive targets for oncotherapy [72]. Pan and his colleagues suggested that pterostilbene (80 μM)-treated human AGS gastric carcinoma cells were markedly arrested at the G0/G1 phase [33]. Upon 80 μM pterostilbene treatment, the degree of phosphorylation of Rb protein, mediated by the down-regulation of cyclin A, cyclin E, CDK2, CDK4 and CDK6 levels, was decreased [33]. However, the expression of p53, p21, p27, p16, GADD45 and CHOP were significantly upregulated, thus maintaining the cell cycle checkpoints and blocking abnormal mitosis [33]. Interestingly, treatment of NSCLC A549 cells cultured in FBS-free medium with lower pterostilbene (5 and 10 μM) concentration induced S-phase arrest through activating the Ataxia Telangiectasia and Rad3-related protein (ATR)/Ataxia telangiectasia mutated (ATM) kinase activity thus subsequently phosphorylating checkpoint kinase 1/2 (CHK1/2), leading to the activation of downstream effector molecules, including p53, followed by activation of the replication stress response [69]. However, the level of p21 implicated in G1 arrest had no change [69]. Nevertheless, the mechanisms by which pterostilbene induces the G1 phase arrest at high doses (usually greater than 50 μM) [69] and S

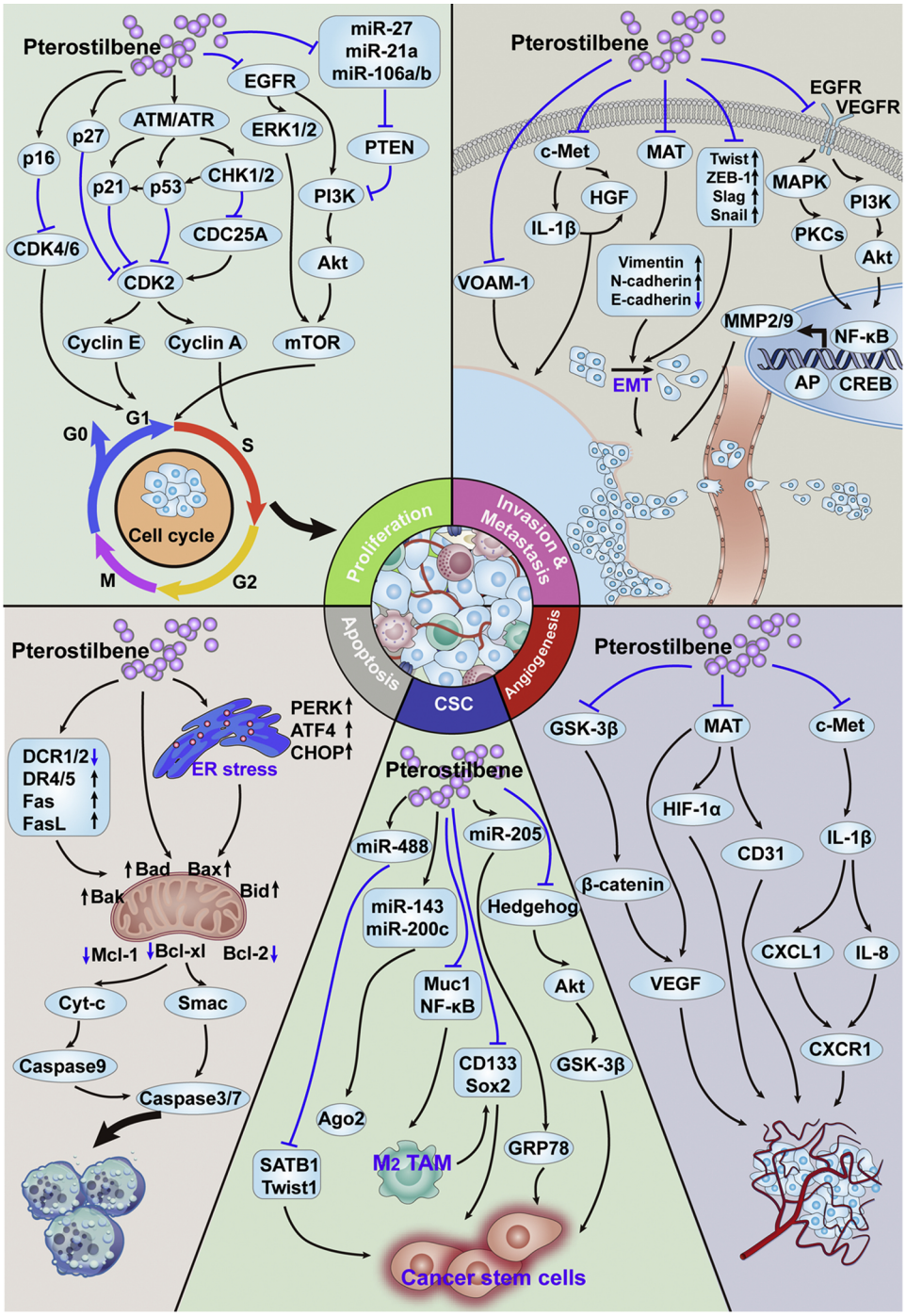

Fig. 2. Proposed oncostatic actions of pterostilbene on the hallmarks of cancer. Abbreviations: Ago2, Argonaute 2; Akt, protein kinase B; AP, activator protein; ATF4, activating transcription factor 4; ATM/ATR, Ataxia telangiectasia mutated/ Ataxia Telangiectasia and Rad3-related protein; Bad, bcl-Associated Death Protein; Bak, bcl-2 homologous antagonist-killer protein; Bax, Bcl-2 associated X protein; Bcl-xl, bcl-X Protein; Bcl-2, B-cell lymphoma-2; Bid, BH3 interacting domain death agonist protein; CDC25A, cell division cycle protein A; CDK2, cyclin-dependent kinases 2; CHK1/2, Checkpoint Kinase 1/2; CHOP, C/EBP homologous protein; c-Met, mesenchymal-epithelial transition factor; CREB, AMP response element binding protein; CSC, cancer stem cell; CXCL1, chemokine (C-X-C motif) ligand 1; CXCR1, interleukin (IL)-8/C-X-C chemokine receptor 1; Cyt-c, cytochrome c; DCR1/2, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors 3/4; DR4/5, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors 1/2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERK1/2, extracellular signal regulated kinases 1/2; ER stress, endoplasmic reticulum stress; Fas, factor associated suicide; FasL, factor associated suicide ligand; GRP78, glucose regulated protein 78; GSK-3β: glycogen synthase kinase-3; HGF, hepatocyte-growth factor; HIF-1α, hypoxic response transcription factor-1α; IL-1β, interleukin-1β; MAPK, mitogen-activated protein kinase; Mcl-1, myeloid cell leukemia-1; MMP-2, matrix metalloprotein-2; MTA1, metastasis-associated protein 1; M_2 TAM, M_2-polarized tumor-associated macrophage; mTOR, mammalian target of rapamycin; Muc1, mucin 1; NF-κB, nuclear factor kappa B; PERK, PKR-like ER kinase; PI3K, phosphoinositide 3 kinase; PKC, protein kinase C; PTEN, phosphate and tension homology deleted on chromsome ten; SATB1, special AT-rich sequence-binding protein 1; Smac, second mitochondria-derived activator of caspase; Sox2, sex-determining region Y HMG-box 2; VCAM-1, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor.

phase arrest at low concentrations remain unclear, thus warranting further investigation. In addition, it has also been reported that pterostilbene provoked S-phase arrest in large B-cell lymphoma cells through significantly increasing the phospho-histone H2AX and CHK2 proteins expression and decreasing the CDC25A, CDK2 and cyclin A2 levels [34]. Moreover, pterostilbene also decreased the cyclin D1, β-catenin and c-MYC expression in HT-29 colon cancer cells [31]. It was demonstrated pterostilbene reduced miR-17, miR-21a and miR-106a/b, and in turn repressed proliferation of prostate cancer DU145 and 22Rv1 cell lines by restoring PTEN expression through inhibiting the phosphorylation of Akt [25,68].

4.2. *In vivo studies*

Pterostilbene has been reported to suppress the urethane-caused lung tumor growth in mice via decreasing the expression of EGFR and resulting in a significant inhibition of Akt/mTOR and ERK1/2 pathway, ultimately leading to disrupt the G1/S transition [23,68,73]. Moreover, Paul et al. revealed that pterostilbene reduced a cell proliferation marker, PCNA, and the β-catenin and cyclin D1 expression in the colon adenocarcinomas in azoxymethane-injected male F344 rats [31] (Fig. 2). In accordance with these studies, it is obvious that pterostilbene could effectively inhibit cancer cell proliferation via a series of signaling pathways.

5. Effect of pterostilbene on cancer cell apoptosis

Apoptosis, a well-known mechanism of programmed cell death, is considered as a natural barrier during tumorigenesis and an important therapeutic target [4,67,74]. Pterostilbene treatment could induce apoptosis in numerous cancer cells, including bladder [10,75], lung [6,76], breast [8,26,68,71,77–79], colon [32,80], gastro [33], pancreas [81,82], oral cavity [83], esophageal [36], cervical [84], melanoma [28], multiple myeloma [9], lymphoma [34,35]. Herein, we summarized the mechanisms of pro-apoptotic effects exerted by pterostilbene in vitro studies.

5.1. The intrinsic pathway

The Bcl-2 family of proteins are the most vital regulators involved in the intrinsic pathway, which are key regulators of apoptosis [85]. It was reported pterostilbene application significantly upregulated the expression of Bax [26,34,68,80], Bak [80], Bad [33,80] and Bid [33,80], downregulated Bcl-2 [8,26,34,68,75], Bcl-xl [26,68,75] and Mcl-1 [26,68], and decreased mitochondrial membrane potential [9,26,33,34,71,81,82]. Afterwards, the release of cytochrome c and second mitochondrial derived activator of caspase (Smac/DIABLO) from the intermembrane mitochondrial space into the cytosol was increased [81]. Upon their release into the cytosol, Smac/DIABLO and cytochrome c induced the activation caspase 9 and caspase 3, thus leading to apoptosis [9,33,34,81,83].

5.2. The extrinsic pathway

The extrinsic pathway is triggered by factor-related suicide (Fas) death receptor, subsequently, which activates downstream caspases and ultimately results in apoptosis [85,86]. Pterostilbene increased the Fas and FasL expression in the human T lymphoma HUT78 cells [10,35], human AGS gastric cancer cells [10,33] and azoxymethane-treated mice [32]. Moreover, pterostilbene could upregulate the expression of TRAIL receptors 1 (DR4) and 2 (DR5), downregulate DcR-1 and DcR-2 expression [79] and activate caspase 3/7/8 [9,28,33,34,76,78,83], thus enhancing the extrinsic apoptotic pathway in cancer cells.

5.3. The endoplasmic reticulum stress pathway

The endoplasmic reticulum (ER) is a vital cytosolic compartment for proteins folding and modification, Ca^{2+} storage and lipids synthesis [6,87,88]. Tumors are often challenged by hypoxia and nutrient deprivation, which perturb the ER, thus leading to ER stress (ERS) [6,87,89]. However, persistent ERS is able to break the balance towards apoptosis and results in cell death [87]. Furthermore, previous studies suggested that pterostilbene, a potent ERS activator [90], induced apoptosis-related cell death via activating ERS in cancer cells [6,36,79,84,90]. Ma et al. reported that the pterostilbene treatment could promote ERS activation via increasing p-PERK, ATF4 and CHOP levels, leading to the ER Ca^{2+} efflux into cytoplasm, thus enhancing lung cancer PC9 and A549 cells apoptosis [6] (Fig. 2). Moreover, pterostilbene induced ROS generation, activated ERK1/2 and p38, upregulated CHOP and then increased the DR4 and DR5 levels, ultimately potentiated TRAIL-induced cell death in the triple negative breast cancer cells with TRAIL-resistant [79]. Experimentally, pterostilbene was proven to induce esophageal cancer EC109 and TE1 cells apoptosis via rise of GRP78, p-PERK, ATF4, and CHOP expression [36]. Furthermore, pterostilbene triggered ERS by redox homeostasis imbalance and consequently led to apoptosis [84]. Thus, above evidence suggests that pterostilbene can promote cancer cells apoptosis, making it be a potential anticancer drug for cancer therapy.

6. Effect of pterostilbene on cancer invasion and metastasis

6.1. In vitro studies

About 90% tumor-associated deaths are correlated with metastatic diseases instead of primary tumors [91,92]. Current evidence has demonstrated that pterostilbene suppressed cancer invasion and metastasis [17–19,24,32,34,37,93–96]. Epithelial-mesenchymal transition (EMT) is a well-known biological process that transforms the polarized epithelial cell into the cell phenotype of mesenchymal [97,98]. There are 3 types of EMT and the third EMT type functions in the tumorigenesis, related to tumor progression and metastasis [97]. Studies have proposed stimulation of EMT was the crucial mechanism for the progression of carcinomas to a metastatic stage [97,99]. Furthermore, studies have reported pterostilbene reversed the EMT [17,18]. Pterostilbene inhibited EMT by the reduction of the mesenchymal protein levels, such as vimentin and N-cadherin, and increase of junctional protein E-cadherin via the inhibition of transcriptional factors (e.g., Snail, Slug, ZEB1 and Twist), in breast cancer MDA-MB-231 and MCF7 cells [17,18].

Matrix metalloproteinases (MMPs), which degrade the extracellular matrix (ECM) and the basement membrane, are intensively correlated with cancer invasion and metastasis [19,100]. Pterostilbene resulted in reductions of MMP-2 and MMP-9 [19,32,34,37], which are most related to cancer invasion and metastasis [37,101]. Moreover, pterostilbene exhibited a potent anti-invasive and anti-metastatic action against 12-O-tetradecanoylphorbol 13-acetate (TPA)-mediated metastasis of human hepatocellular cancer cells via suppressing MMP-9 gene expression by PKC, EGF and VEGF downregulation, then blocking the phosphorylation of MAPK and PI3K/AKT and inhibiting NF-κB and AP-1 activity [37]. In human oral squamous cell carcinoma (SCC)-9 cells, pterostilbene inhibited the activation of Akt, ERK1/2 and JNK1/2, and then affected transcriptional inhibition of MMP-2 and urokinase-type plasminogen activator (u-PA) through suppressing NF-kB, CREB and SP-1 nuclear translocation and MMP-2 and u-PA promoter binding activities, thus resulting in migration/invasion capacities inhibition in SCC-9 cells [96]. Pterostilbene can repress the invadopodia formation and maturation via the reduction of PDGFR-α, c-Src kinase, cortactin, and tyrosine kinase substrate with five Src homology 3 domains (Tks5) expression and inhibit the accumulation of membrane type 1-matrixmetalloproteinase (MT1-MMP) and reduce the MMP-2/9 secretion, leading to the inhibition of cell invasion and migration in breast cancer MDA-MB-231 cells [19].

Pterostilbene treatment markedly phosphorylated Akt and subsequently downregulated ERK phosphorylation in suspended Lewis lung cancer cells, then significantly reduced polymeric fibronectin (polyFN) due to the repression of transportation of intracellular monoFN into the extracellular plasma membrane of cancer cells and concomitant polymerization into polyFN [21]. Of note, it was reported that the c-Met activation preferentially accelerated brain metastases in breast cancer patients via promoting cancer cells adhesion to the brain endothelial cells. Moreover, c-MET could stimulate the secretion of IL-1β and then induce cancer-associated astrocytes to secrete the c-Met ligand HGF [16]. However, pterostilbene suppressed the c-Met pathway by significantly decreasing c-Met mRNA expression, thus inhibiting brain metastasis [16] (Fig. 2). Additionally, pterostilbene inhibited the proliferation of the highly malignant B16 melanoma. Pterostilbene treatment could decrease the level of vascular adhesion molecule 1 in hepatic sinusoidal endothelium, thus consequently reducing B16M-F10 cell adhesion to the endothelium [29,30].

6.2. In vivo studies

Inhibiting EMT of pterostilbene was further evaluated in vivo studies. Pterostilbene is able to inhibit EMT through downregulating the vimentin, Src, Slug, Twist and ZEB1 expression in MDA-MB-231 cell

tumor xenograft [17]. Nuclear metastasis-associated protein 1 (MTA1) is a part of the nucleosome remodeling and deacetylase (NuRD) corepressor complex that is correlated with gene silencing and histone deacetylation [102]. Moreover, the overexpression of MTA1 was involved in the progression of prostate cancer and promoted the EMT-related tumor metastasis [24,93–95]. Interestingly, it was reported that pterostilbene treatment could decrease multi-organ (prostate, lung, liver and kidney) metastasis through inhibiting MTA1 in prostate cancer [94]. Research has shown pterostilbene markedly mitigated tumor growth and spontaneous metastasis by downregulating MTA1 in prostate cancer DU145 xenograft mouse model [103]. Furthermore, pterostilbene reduced MTA1 protein levels leading to increase of E-cadherin and decrease of vimentin in prostate-specific Pten-loss mouse models [24]. These studies collectively demonstrate that pterostilbene has the potency to decrease the malignancy of tumor via repression of tumor metastasis, providing new insights into possible therapeutic interventions.

7. Effect of pterostilbene on cancer angiogenesis

7.1. In vitro studies

Tumor angiogenesis results from the enhancement of pro-angiogenic factors such as VEGF and downregulation of anti-angiogenic factors (e.g., angiostatin and endostatin) [104]. Coined in the late eighties, the term “angiogenic switch” refers to a time-restricted event during cancer progression where the balance between pro- and anti-angiogenic factors tilts towards a pro-angiogenic outcome [105], which is affected by pterostilbene [16,24,27,32,38]. Current evidence has demonstrated that pterostilbene inhibited the production of VEGF [28,32], the most important positive regulatory factor [47]. Butt and his colleagues reported that cotreatment of pterostilbene with histone deacetylase inhibitor vorinostat resulted in a significant decrease of MTA1-associated proangiogenic factors (HIF-1α, VEGF, and IL-1β) in prostate cancer cell lines [27]. Therefore, cotreatment with pterostilbene with chemotherapeutics may have more effective actions but less side-effects through targeting MTA1-associated angiogenesis [27]. Pterostilbene markedly repressed the growth of PDGF-activated vascular smooth muscle cells through Akt inhibition [38]. Therefore, it puts forward a new research direction that whether pterostilbene can provoke the same effect in vessel of cancer. On the other hand, activation of c-Met strengthens angiogenesis via IL-8 and CXCL1 enhancement; however, pterostilbene exhibited stronger efficacy on inhibiting the c-Met expression and significantly inhibited the IL-1β, IL-8 and CXCL1 expression in human breast carcinoma 231BrM cell line [16].

7.2. In vivo studies

Consistent with above-mentioned study, pterostilbene inhibited AOM-induced β-catenin activation via repressing AOM-induced GSK-3β phosphorylation, thus strongly decreased the level of VEGF in AOM-treated male ICR mice [32]. It is noteworthy that pterostilbene treatment results in the inhibition of hemangiogenesis, as confirmed by decrease of CD31, VEGF-C and IL-1β due to MTA1 inhibition in the prostate tissues of $PTEN^{+/f}$ prostate-specific heterozygous mice [24] (Fig. 2). Considering the data discussed, it’s definite that pterostilbene exerts inhibitory effects on angiogenesis. Nonetheless, researches in this regard remain insufficient and the mechanism of pterostilbene in cancer angiogenesis warrants further investigation.

8. Effect of pterostilbene on cancer stem cell

Cancer stem cells (CSCs) are a group of cancer cells with the ability to self-renew and differentiation [41,106,107]. Additionally, CSCs are considered to be intensively related to tumor metastasis, recurrence and anticancer drug resistance [108,109]. There is solid evidence that pterostilbene inhibited multiple CSCs, including breast CSCs [18,20,41,68,110–112], glioma CSCs [42], and lung CSCs [22]. Pterostilbene selectively repressed $CD44^{+}/CD24^{-}$ CSCs in MCF-7 cells [41,110]. Pterostilbene reduced the stem cell marker CD44 level in breast CSCs and augmented β-catenin phosphorylation through decreasing expression of hedgehog protein and Akt and GSK-3β phosphorylation. Therefore, pterostilbene treatment reduced c-Myc and cyclin D1 expression and then decreased the stemness activity [41,110]. In lung cancer A549 and H441cells, pterostilbene treatment decreased the $CD133^{+}$ lung cancer cell numbers in the presence of tumor-associated macrophages (TAMs) through MUC1, NF-κB, β-catenin, Sox2, and CD133 downregulation [22].

Study has suggested that pterostilbene treatment inhibited the stemness of GSCs via downregulating the GRP78, c-Myc, β-catenin and vimentin levels by the miR-205 upregulation in human glioblastoma GBM8401 cell line [42]. Furthermore, pterostilbene activated the Argonaute2 (Ago2), a central RNA interference (RNAi) component, which thereby represses breast cancer stem-like cell characteristics through upregulating the tumor-suppressive miR-143, and miR-200c levels in MDA-MB-231-luc-D3H2LN cells [20,68]. Intriguingly, pterostilbene may reduce CSCs by suppressing EMT, given that activation of the EMT program is able to confer upon carcinoma cells stem cell characteristics [113–116]. It was identified pterostilbene impaired M2-tumor-associated macrophage-induced proliferation and metastatic capacity of breast CSCs through downregulating NF-κB expression and then upregulating amount of an anti-metastatic miR488, which subsequently decreased the expression of SATB1 and Twist1 in both M2 TAM-cocultured breast cancer cells [18,112] (Fig. 2). Hence, research should be carried out to test the ratiocination.

9. Pterostilbene and immunotherapy

Immunotherapy has emerged as an important anticancer strategy in recent years [117,118]. Enhancing anticancer immunity is regarded as an effective means of repressing cancer progression [4,119]. The human cathelicidin antimicrobial peptide (CAMP) gene, expressed by both immune and epithelial cells, is an ideal candidate for killing a wide range of bacteria and giving a practicable approach for strengthening the innate immune response [39,120]. In experimental studies, pterostilbene promoted the expression of CAMP protein in both myeloid leukemia U937 cell and keratinocyte HaCaT cell [39]. Moreover, cotreatment of pterostilbene with $1\alpha,25(OH)_2D_3$f further upregulated the CAMP expression [39]. Therefore, it is the first time to demonstrate that pterostilbene may enhance the innate immune ability via promoting CAMP [39].

Of note, vascular abnormality may facilitate immune evasion through abnormal immune responses [118,121]. It was put forward that combining antiangiogenic strategies and immunotherapies might upregulate the effectiveness of immunotherapy and attenuate the immune-related side-effects, particularly antiangiogenic agents combined with immune-checkpoint inhibitors [118,122]. Pembrolizumab and ipilimumab, T-cell-associated checkpoint inhibitors, have been currently approved by European Medicines and Agency U.S. FDA [40,123]. Pembrolizumab and ipilimumab respectively inhibit the PD-1 pathway and the cytotoxic T-lymphocyte-associated protein 4 (CTLA4), prevailing in recent cancer therapies [40,123,124]. Therefore, it is worthwhile to investigate the combinatorial effect of pterostilbene and immune-checkpoint inhibitors, such as pembrolizumab and ipilimumab.

Snail was been recently reported to participate in the activation of immunosuppressive cytokines and regulatory T cells [113,125]. The generation of impaired dendritic cells, Snail-expressing cells and the EMT process are also correlated with resistance to dendritic cell immunotherapy, acting on multiple immunosuppression and immunoresistance mechanisms [113,125]. Accordingly, pterostilbene may

preserve immunocompetence in patients via EMT inhibition. Although these conditions indicate that pterostilbene has an indirect anticancer action on cancer cells through strengthening of anticancer immunity, there still warrants further investigation.

10. Drug synergy of pterostilbene with chemotherapy

10.1. In vitro studies

As one of the dietary phytophenols, pterostilbene appears to be extremely safe. It has favorable bioavailability and pharmacokinetic profile as well as its pharmacological activities [126]. Cotreatment of pterostilbene with chemotherapy could strengthen anticancer actions of agents and decrease their side effects [77,80,127–129]. Current study has suggested that pterostilbene promoted the sensitivity of colon cancer cells to 5-fluorouracil and pterostilbene/5-fluorouracil co-treatment exhibited a more powerful anticancer effect in colon cancer Caco-2 cell line [128]. Intriguingly, treatment of prostate cancer cell lines with pterostilbene and low dose vorinostat led to more powerful repression of MTA1/HIF-1α cascades than by high dose vorinostat alone, indicating the combinatorial strategy provoked higher efficacy and less toxicity [27,130]. Equally importantly, two estrogen receptor–positive breast cancer MCF7 and ZR-75-1 cell lines had additive reduction in cell viability with pterostilbene and tamoxifen cotreatment in low does [77]. However, when pterostilbene combined with aromatase inhibitor anastrozole, only ZR-75-1 cells showed additive cell viability inhibition [77]. A recent study found that the addition of pterostilbene to megestrol acetate led to a synergistic proliferative repression in cancer cell through further attenuation of cell cycle and survival pathways and inhibition of MAPK/ERK cascades in the endometrial cancer HEC-1A cells [131].

Cotreatment of pterostilbene with plant-derived agents exhibits more potent anticancer effects [28,41,110,127,132–134]. Pterostilbene and 6-shogaol could upregulate the anticancer activity of paclitaxel in MCF-7 breast cancer cells [41,110]. Moreover, when combined with curcumin and its analogues, pterostilbene treatment exhibited significant potential to alleviate LOX-mediated activity in E40 cells derived from Hep 3B cell line [133]. It has also been documented that pterostilbene plus (-)-epigallocatechin-3-gallate had additive antiproliferative effects and altered the apoptotic mechanisms in both pancreatic cancer MIA PaCa-2 and PANC-1 cells [134]. Besides, cotreatments of pterostilbene and inositol-6-phosphate, a complex carbohydrate, engendered a more profound level of proliferative suppression and VEGF production in the human melanoma SK-MEL-2 cell line [28]. Cotreatment of astragalus and pterostilbene engendered more profound growth inhibition compared with either treatment alone in the melanoma SK-MEL-2 cells [132].

The effects of several other chemotherapeutic drugs combined with pterostilbene also have been explored [6,129,135]. Pterostilbene co-treatment with THA significantly increased Bax, Caspase 3, p53, CHOP and ROS level, and decreased Bcl2 protein compared with either treatment alone in lung cancer PC9 and A549 cells [6]. In addition, pterostilbene is able to enhance the anticancer effects of the EGFR inhibitor gefitinib and sertraline in glioblastoma multiforme cells [129,135]. Cotreatment with either of these two compounds with pterostilbene significantly suppressed cell proliferation and metastasis via MAPK inhibition [129]. On the other hand, therapy-induced senescence can be achieved at far lower chemotherapeutic doses than those required to induce apoptosis, thus decreasing the side effects of anticancer therapy [5,136]. Additionally, as cancer cells often evoke resistance to apoptosis, pro-senescence therapy has recently emerged as a novel method to treat cancers [5,137]. Emerging evidence suggests that pterostilbene is a promising senescence-inducing drug on cancer cells [5], thus enhancing anticancer activities and reducing adverse actions of chemotherapy [5,138].

10.2. In vivo studies

Studies have shown pterostilbene sensitized tumor cells to vorinostat, a histone deacetylase inhibitor, leading to prostate cancer growth repression in the Pten-null mouse [27]. Additionally, pterostilbene and megestrol acetate cotreatment markedly inhibited the tumor growth in the endometrial cancer HEC-1A xenograft mouse model [131]. Singh et al. observed that a combined treatment of pterostilbene with lupeol were more effective to decrease tumorigenesis, ROS generation in male Swiss albino mice treated with benzopyrene [127]. Moreover, pterostilbene co-treatment with THA significantly enhanced the regulation of apoptosis-related proteins and upregulated CHOP level and ROS generation compared with either treatment alone in PC9 xenografts athymic nude mice [6]. The combination of pterostilbene + QUER + X-rays + FOLFOX6 regimen in HT-29 tumor-bearing mice was more effective and markedly promoted tumor regression [80]. These studies collectively provide the basic results of the potential of pterostilbene with chemotherapy for the cancer treatment. However, further studies should focus more on clinical trials.

11. Pterostilbene and radiotherapy

11.1. In vitro studies

Despite the fact that radiotherapy is used to treat up to 50% of cancer patients and to cure 40% of patients [139], many patients still suffer from tumor recurrence and adverse-effects after radiotherapy [140]. Therefore, to enhance the anticancer actions and to reduce the side-effects of radiotherapy are essential [140]. Several solid cancer CSCs were recently reported to particularly resist radiotherapy [141–147]. As mentioned above, pterostilbene can inhibit multiple CSCs through multiple signal pathways, thus leading to improvement of radiotherapy. CD133-positive glioma stem cells usually lead to glioma radio-resistance and cancer recurrence [42,143]. Interestingly, pterostilbene could enhance the GBM cells sensitivity to 5 Gy γ-irradiation in human glioblastoma GBM8401 cells [42]. Proverbially, it is recognized that DNA damage and reactive free radicals lead to the harmful effects of ionizing radiation [4,148]. Pterostilbene could decrease ROS generation and prohibit oxidative stress via upregulating various antioxidants expression [149]. Equally importantly, pterostilbene also could alleviate inflammatory response via inhibiting the inflammatory factors [49]. Given that pterostilbene is well-recognized antioxidant and anti-inflammatory [149], it is worthwhile to carry out research to reveal the radioprotective role of pterostilbene.

11.2. In vivo studies

It was reported that GBM8401 cell tumor xenograft that received the pterostilbene/irradiation (10 Gy once) cotreatment displayed the smallest tumor volumes, when compared with the irradiation or pterostilbene treatment alone group [42]. The result supported the hypothesis that pterostilbene could enhance the efficiency of irradiation [42]. Moreover, Sirerol et al. provided the evidence associated with pterostilbene-exhibited protection against electromagnetic radiation by UVB in SKH-1 hairless mice [66]. However, it still warrants further basic studies to verify the roles of cotreatment between pterostilbene application and radiotherapy before stepped into clinical trials.

12. Pterostilbene and clinical applicative research

Although pterostilbene possesses the anticancer effects on a variety of neoplasms, its applications was still strictly restrained by the limited solubility and stability [150]. Studies on blood pharmacokinetics of rats showed that application of isoleucine prodrug with pterostilbene could enhance its absorption and decrease its metabolism in the blood [151]. Experiments also found that the prodrug had prospective human

intestinal absorption profiles in Caco-2 cells [151]. Moreover, it is well-known that encapsulation of natural compounds into the nanocarriers could enhance their bioavailability [49,152]. Additionally, the FDA has already confirmed their safety application in human bodies [49]. Liposomal targeting strategy may allow the use of higher doses of drug without side-effects; and targeted drug delivery may increase the drug concentrations in neoplasms [153]. Zhang and his colleagues reported the nanoemulsion delivery system developed by using low-energy emulsification method markedly improved the pterostilbene's stability and solubility [150]. Pterostilbene solubility in water was dramatically strengthened up to 2000 times by nanoemulsions through using isopropyl myristate, olive oil and flaxseed oil. Moreover, the bioavailability of pterostilbene was almost up to 100% in 24 h at pH = 3.6 with isopropyl myristate emulsion and its metabolism was further inhibited [49].

Neves et al. developed two novel resveratrol nanodelivery systems, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). The two carriers were considered as suitable for oral administration with a controlled release after uptake [154]. Given that pterostilbene is the derivative of resveratrol, the study may provide references for research of pterostilbene nanodelivery systems. Furthermore, a variety of means of drug packing for delivery have been invented, such as Gold nanoparticles (GNPs) [155], Poly(lactic-co-glycolic) acid (PLGA) [156,157], magnetically responsive nanocarrier [158] and exosomes [159]. These above strategies may be similarly exerted in the future pterostilbene administration.

13. Discussion and conclusions

Despite the oncostatic actions of pterostilbene regarding the hallmarks of cancers, more concerns should also be placed on the drug safety. In a study done by RUIZ and his colleagues, mice were fed with the doses of pterostilbene up to 3000 mg/kg/day for 28 days, which are equivalent to 500 times of the estimated mean human polyphenols intake (25 mg/day). Furthermore, it is noteworthy that mice had no toxic effects or mortality [160]. Moreover, compared with control groups, upregulated red blood cell number and the hematocrit were observed in pterostilbene administrated groups, but there were no significant changes in biochemical parameters and clinical signs [160]. It was concluded that pterostilbene is generally safe for human use, and the doses could conduct up to 250 mg/day in a clinical study [131,161]. In the light of the biological safety of pterostilbene and the results of its oncology and animal experiments, more clinical trials should be carried out to clarify the reasonable therapeutic dosages of pterostilbene and its exact role in the effect of chemotherapy and radiotherapy as an adjuvant.

Pterostilbene is significantly more bioavailable than resveratrol [8], due to the presence of twomethoxy groups [14,15]. At present, resveratrol has been extensively studied and its basic research direction and mechanism in tumor can provide reference for the research of pterostilbene [8]. In recent studies, a pterostilbene derivative, pterostilbene carboxaldehyde thiosemicarbazone (PTERC-T) has been synthesized with improved activity than pterostilbene [54,162–166]. Nikhil et al. reported that PTERC-T application significantly reduced the tumor volumes in Ehrlich ascitic cell xenograft [166]. In addition, PTERC-T treatment promoted apoptosis via the caspases activation through inhibiting Akt and ERK pathways in MCF-7 cells [166]. Moreover, a novel pterostilbene derivative, ANK-199, induced autophagic cell death through enhancing the expression of LC-III and beclin1 in cisplatin-resistant CAR human oral cancer cells [167]. Additionally, compared with pterostilbene, another analogue 3′-hydroxypterostilbene (HPSB) exerted more potent of anticancer actions on inducing apoptosis and inhibiting proliferation in vitro [168]. The study demonstrated that the bioactivity difference of HPSB compared with pterostilbene was associated with the presence and position of hydroxyl groups on the basic pterostilbene chemical structure [168]. In summary, these results shed some light on the potential possibility of discovering unique chemical modifications on pterostilbene to exert stronger anti-cancer and anti-metastatic efficacies in the future.

In conclusion, pterostilbene may be a potent anticancer agent for various cancer treatments. Furthermore, pterostilbene, through its activities of anti-proliferation, pro-apoptosis, anti-invasion and metastasis, anti-angiogenesis, and inhibition of cancer stem cell, should be given more attention as a powerful oncostatic drug. Since pterostilbene application potentiates the efficacy and decreases the adverse effects of chemoradiotherapies and has the potential to augment the immunotherapy, and it could be used combined with conventional treatments thereby enhancing their oncostatic effectiveness. Inasmuch as pterostilbene has no toxic effects and poor solubility and stability, further clinical trials which include pterostilbene and chemical modification or conjugation with nanoparticles that help pack and deliver pterostilbene into tumor tissues will help to facilitate better applications of pterostilbene in the field of cancer therapy. Therefore, employing pterostilbene as a complementary and alternative medicine may be a prevailing therapeutic strategy against cancer malignancy. However, more clinical trials are required to validate the potential anticancer activities of pterostilbene before its wide clinical use.

Conflict of interest

The authors declare no competing interests regarding the publication of this manuscript.

Authors' contributions

YXL, HJ and LXF designed the study. MZQ, ZXY, XLQ and LD searched the literature and wrote the manuscript. DSY, LWM, ZJ and ZHM searched the literature and made the table, and MZQ draw the figures. All authors read and approved the final manuscript.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81572252, 81871866), Natural Science Foundation of Shaanxi Province (2016SF-308; 2019SF-033), Project of Tangdu Hospital, The Fourth Military Medical University (2015 Key Talents; 2018 Key Talents), and the Excellent Doctoral Support Project of the Fourth Military Medical University (2018D09).

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