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Review

Occurrence, Bioavailability, Anti-inflammatory, and Anticancer Effects of Pterostilbene

Wei-Sheng Lin, Jane Valorie Leland, Chi-Tang Ho,* and Min-Hsiung Pan*

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ABSTRACT: Supplementation with natural compounds found in fruits and vegetables has long been associated with a reduced risk of several types of cancer. Pterostilbene is a natural stilbenoid and a dimethylated analogue of resveratrol which is found primarily in blueberries. Pterostilbene exhibits a range of pharmacological properties, particularly anti-inflammatory and anticancer effects. Due to two methoxy groups in its skeleton, pterostilbene is more lipophilic than resveratrol and thus possesses higher intestinal permeability and cellular uptake and enhanced stability. Moreover, pterostilbene exhibits less toxicity and fewer adverse effects, providing it with superior potential in cancer chemoprevention and chemotherapy applications. Numerous research studies have demonstrated that pterostilbene possesses detoxification activities, mediating the anti-inflammation response, regulating the cell cycle, augmenting apoptosis, enhancing autophagy, and inhibiting tumor angiogenesis, invasion, and metastasis by modulating signal transduction pathways which block multiple stages of carcinogenesis. In this review, we illustrate that pterostilbene is a natural compound having bioavailability. The extensive metabolism of pterostilbene will be discussed. We also summarize recent research on pterostilbene's anti-inflammatory and anticancer properties in the multistage carcinogenesis process and related molecular mechanism and conclude that it should contribute to improved cancer management.

KEYWORDS: *pterostilbene, bioavailability, chemoprevention, anti-inflammation, anticancer*

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INTRODUCTION

Cancer development in an organism involves a dynamic change in the genome, a multistep and long-term process that involves three critical steps (initiation, promotion, and progression), which ultimately lead to cancerous cell invasion and metastasis. This slow, stepwise development is influenced by many complex factors, including family history, aging, the carcinogenic agents involved, dietary habits, obesity, circadian rhythms disruption, and chronic inflammation.[1,2] Inflammatory responses, in particular, play a critical role in tumor development, impacting every single step in tumor formation. For instance, an inflammatory microenvironment can increase the frequency of new mutations, thus enhancing the proliferation of mutated cells.[3,4] Fortunately, many epidemiological studies and clinical trials are being conducted on the use of natural dietary supplements and nutritionally modified diets to prevent cancer. Moreover, the literature has demonstrated that chemo-preventive phytochemicals can block or reverse the premalignant stage in multistep carcinogenesis or at least retard the development of precancerous cells into malignant cells. Thus, chemoprevention is a promising strategy for preventing cancer.[5,6]

Pterostilbene (3,5-dimethoxy-4′-hydroxy-*trans*-stilbene) is a natural phenolic compound and a dimethylated analogue of resveratrol which has been studied extensively. Studies have revealed that it possesses antidiabetic, antihyperlipidemic, antiatherosclerotic, antihypertensive, anticardiovascular disease, antiobesity, and antisteatosis activities.[7−13] Furthermore, pterostilbene has been shown to have potent biofunctionalities in anti-inflammatory and anticancer processes.[14−16] Its dimeric structure indicates that its oxidation reaction takes place at the 4′-OH position of the hydroxystilbenic moieties. Many dimeric products have been found due to the ability of electron-delocalized radicals to couple at various sites, resulting in its multibiofunctionality.[17] Due to structural methoxylation at the 3 and 5 positions, pterostilbene is lipophilic, increasing intestinal absorption and contributing to a higher potential for biological uptake.[18−20] In terms of safety, pterostilbene has few, if any, toxic side effects and is classified as low risk. It is safe for use in doses of up to 250 mg/day, according to human clinical trials.[21,22] Thus, pterostilbene has attracted considerable attention in terms of chemopreventive activities against cancer.[14,15]

In this review, we first summarize pterostilbene occurrences in nature and its bioavailability. Then, we will illustrate pterostilbene's anti-inflammatory and anticarcinogenic roles in different steps of cancer development and discuss the related cellular signaling pathways during carcinogenesis. Finally, we will describe how pterostilbene can be combined with other cancer chemopreventive phytochemicals for potential cancer treatment.

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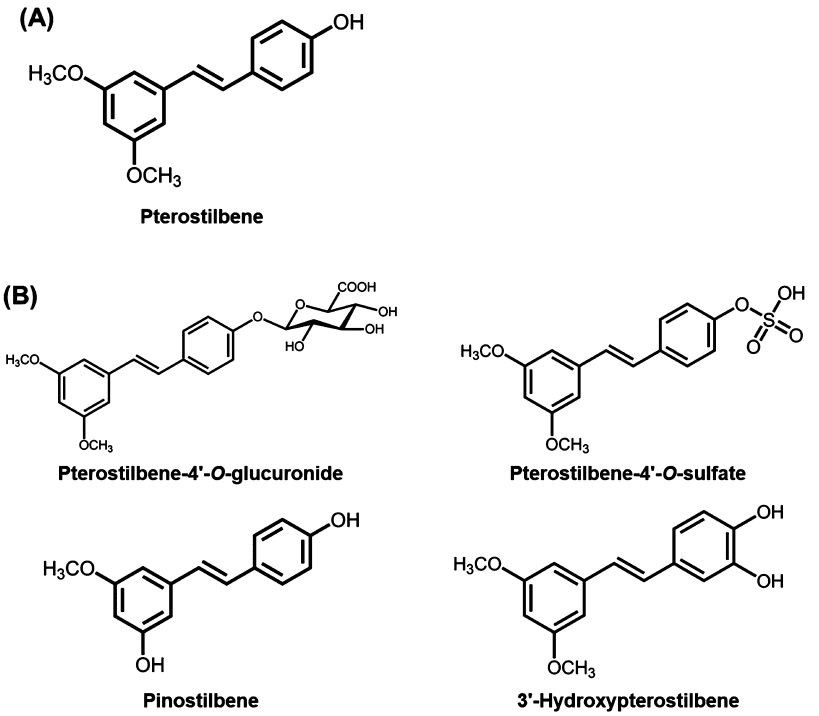

Figure 1. Selected chemical structures of pterostilbene (A) and pterostilbene metabolites (B). Pterostilbene (3′,5′-dimethoxy-4-hydroxystilbene) is a dimethylated analogue at the 3 and 5 positions of resveratrol. The representative of the characterized compounds of pterostilbene such as pterostilbene-4′-*O*-glucuronide and pterostilbene-4′-*O*-sulfate. Those are the major routes to eliminate from the human body. Pinostilbene was through demethylation formation from pterostilbene, it is speculated by gut microbiota demethylases biotransformation product. 3′-Hydroxypterostilbene, one of the metabolites of pterostilbene isolated from the whole plant of the herb *Sphaerophysa salsula*. Pinostilbene and 3′-hydroxypterostilbene both are found to have potent biofunctionalities.

Natural Occurrence and Derivatives of Pterostilbene. Pterostilbene is one of the stilbenoids belonging to the polyphenolic compounds (Figure 1). It is also a phytoalexin that is synthesized in plants as a secondary metabolite in response to environmental stresses such as microbial or fungal (*Plasmopara viticola*) infestation and exposure to ultraviolet light or heavy metal.[23−25] It was first isolated from the heartwood of the red sandalwood (*Pterocarpus santalinus*) tree in 1940,[26] then found shortly thereafter in grapevines (*Vitis vinifera*) and blueberries.[27,28] In rabbiteye blueberry (*V. ashei* Reade), 9.9−15.1 μg of pterostilbene is present, on average, in every 100 g of dried sample. It can also be found in deerberry (*V. stamineum* L.) at about 52 μg/100 g dry sample.[29] It is noteworthy that in grapes infected by a fungus, there is a higher quantity of pterostilbene in fresh skin (0.2−4.7 μg/g) when compared to that of healthy grapes (14−74 ng/g for *var.* Gamay, and 120−530 ng/g for *var.* Pinot Noir).[30] Because pterostilbene is not abundant in natural sources, Martínez-Márquez et al. devised a metabolic engineering-based strategy to produce resveratrol derivatives using resveratrol-converting enzymes (stilbene synthase resveratrol *O*-methyltransferase). This strategy led to naturally produced pterostilbene.[31]

Bioavailability and Metabolites of Pterostilbene. Bioavailability is a pharmacokinetic term representing the ratio between the dose of a drug and its concentration in body fluids and tissues over time. As the absorbed compound is consumed and becomes available to the target site, it becomes accessible for physiological movement or a therapeutic capacity.[32] Many complex processes besides the drug absorption factor influence the bioavailability exposure dose, for instance gastric acidity, gastrointestinal transit time, the hypertrophy of duodenal villi, hepatic enzyme activity, protein binding, and blood flow.[33,34] It is worthwhile mentioning that the chemical structures of the ingested compounds' themselves influence the rate and extent of absorption, metabolism, and excretion. In pterostilbene, the two methoxy groups in the stilbenoid skeleton create greater hydrophobicity. Based on the current literature, methylated polyphenols have dramatically higher intestinal permeability and enhanced hepatic stability. Hence, lipophilic properties enhance cellular absorption and also limit metabolic clearance in the intestinal epithelial and hepatic cells. Pterostilbene possesses metabolically stable properties based on having only one free hydroxyl group usable for glucuronidation or sulphation.[35] Studies have shown that pterostilbene is therefore more bioavailable than other stilbenoids such as resveratrol, gnetol, piceatannol, and oxyresveratrol, with oral bioavailability rates of 80%, 29.8%, 6.59%, 50.7%, and 9.13%, respectively.[36] A similar result is that pterostilbene has approximately 3- to 4-fold higher bioavailability than resveratrol.[18] The phase II metabolic enzymes and gut microbiota play critical roles in phytochemical biotransformation. It appears that phytochemical metabolites might show different or stronger biological activities than their original molecules.[37−40] A study that examined metabolic profiles found that sulfate and glucuronide conjugates are evident in the results.[18] Wang and Sang's review presents the metabolism of resveratrol and pterostilbene, in which the UDP-glucuronosyltransferase family of enzymes catalyze the formation of pterostilbene-4′-*O*-glucuronide from pterostilbene and glucuronic acid. Moreover, the pterostilbene-4′-*O*-sulfate formed of pterostilbene was catalyzed through the sulfotransferase family of enzymes. Both forms of metabolite

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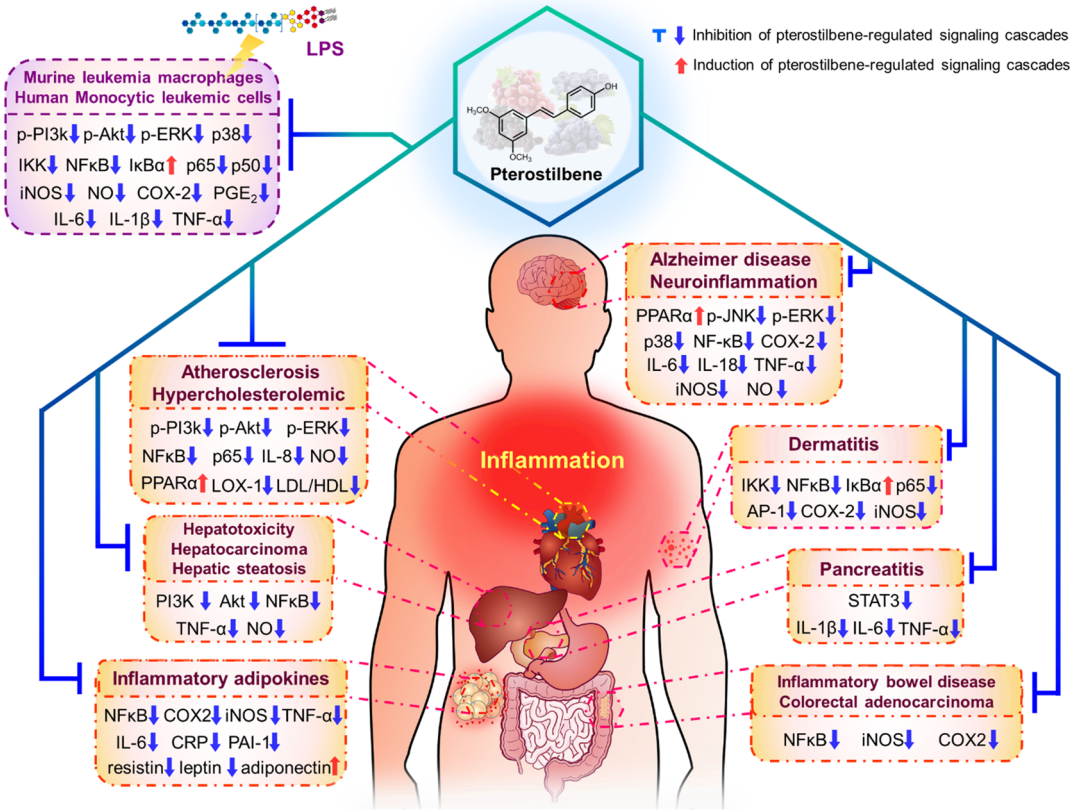

Figure 2. Schematic representation of chemopreventive effects of pterostilbene on inflammation diseases. Pterostilbene could attenuate inflammation-related diseases such as Alzheimer's disease, dermatitis, obesity or metabolic disease-induced inflammatory, pancreatitis, and inflammatory bowel disease, etc. The anti-inflammatory mechanisms of pterostilbene correlate with several signaling pathways and have multiple direct and/or indirect targets by these factors.

biological activity are largely unknown and represent important avenues for further research.[20] Shao et al. study has been demonstrated nine novel mouse urinary pterostilbene metabolites, however, their biological activities was unclear.[41] Pterostilbene revealed antiobesity effect in rats through modulating gut microbiota including enrich *Akkermansia* and *Odoribacter* genus.[8] Moreover, pinostilbene and pterostilbene have been shown to have similar biological activities such as antioxidative,[42] anti-inflammatory,[43] anticancer,[44,45] antimetastasis,[46] and neuroprotection.[47] Additionally, studies have revealed that 3′-hydroxypterostilbene, one of the metabolites of pterostilbene found in the herb *Sphaerophysa salsula*,[48] appears to augment anticancer activity by inhibiting inflammation and tumor cell proliferation as well as inducing apoptosis *in vitro*[49] and *in vivo*.[50,51] Sun et al. also found that pinostilbene is a major metabolite of pterostilbene in the mouse colon.[45]

Anti-inflammatory Activity of Pterostilbene. Inflammation is a well-known complicated biological response to microbial infection, chemical irritation, and tissue injury that aims to eliminate the pathogen or abnormal cells. The inflammatory response triggers signaling cascades and activates transcription factors and gene expression. Ultimately, the immune or inflammatory cells produce and release various oxidants and proinflammatory cytokines. Simultaneously, these inflammatory mediators promote further recruitment of a wide range of immune cells into inflamed sites and there they elicit redness, fever, edema, and pain.[52] Currently, a great deal of evidence points to chronic inflammation increasing the risk of developing cancer. For example, ulcerative colitis and Crohn's disease are associated with colon cancer; prostatitis is connected with prostate cancer. Due to mutant cells accompanying an inflammation microenvironment, oxidative stress, gene mutations, epigenetic changes, inflammatory cytokine-induced cell proliferation, the inhibition of apoptosis, the secretion of proteinases, the expression of adhesion molecules, and angiogenesis drive the malignant transformation.[3,53] Therefore, inhibition of inflammatory signaling is usually recognized as a potential mode for chemoprevention.

As mentioned previously, pterostilbene is a plant phytoalexin polyphenol that functions primarily to protect the plant against pathogens or other environmental stresses. Pterostilbene contributes to a variety of biofunctional properties, in particular, anti-inflammatory and antioxidant properties. Furthermore, several *in vivo* and *in vitro* studies have shown that pterostilbene inhibited chronic inflammation for a wide range of diseases including neuroinflammation, dermatitis, pancreatitis, inflammatory bowel disease, atherosclerosis, and obesity (Figure 2.).[54−59] According to the portion *in vivo* study,[55,65,72] result of conversion of animal doses to human equivalent doses, the dietary intake is approximately 96−480 mg/day in a 60 kg human. Pterostilbene was found to be an agonist for the peroxisome proliferator-activated receptor α (PPAR α) *in vitro*[60] and *in vivo*.[61] Pterostilbene is associated with anti-inflammatory activity due to the induced expression of the inhibitory protein nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα).[62,63] *In vitro*, pterostilbene suppresses the pro-inflam-

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matory cytokines (such as TNFα, IL-1β, IL-6, IL-8, and IL-18) and nitric oxide (NO) production through the inhibition of the nuclear factor kappa B (NF-κB) signaling nuclear translocation[55,64−70] and performs the same service *in vivo*.[71−75] Furthermore, pterostilbene has been demonstrated to downregulate inducible nitric oxide synthase (iNOS) and cyclooxygenase-1 (COX-1) or COX-2, the prostaglandin E2 (PGE_2) gene, or protein levels *in vitro*[66,69,76,77] and *in vivo*.[74,75,78−80] Moreover, it was found that pterostilbene represses the levels of iNOS and COX-2 by inactivating NF-κB or activator protein 1 (AP-1) via blocking the phosphorylation activating the mitogen-activated protein kinase (MAPK) (extracellular signal-regulated protein kinase, ERK1/2 and p38), phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt),[66,70,71,77,78] and jun amino-terminal kinase (JNKs) pathways.[64] In addition, pterostilbene suppresses the p65 nucleus translocation, thus inhibiting NF-κB activity.[70,71,73−75,79] Furthermore, it has been suggested that pterostilbene attenuates inflammatory responses by inhibiting endoplasmic reticulum stress (ERS) signaling in human umbilical vein endothelial cells (HUVECs), inflammatory injuries induced by TNF-α,[81] and potassium dichromate-induced HaCaT skin cell inflammation modes.[82]

Chemopreventive Effects of Pterostilbene in Initiation Stage of Carcinogenesis. The initiation stage in the development of cancer consists of exposure to carcinogens, oxidative stress, or inflammatory injury, which results in the DNA damage, gene mutations, and irreversible genetic alterations, triggering the transformation of normal cells into cancer cells.[83,84] Thus, the inhibition of oxidative stress and inflammation or reduction of the metabolic activation of numerous chemical carcinogens can reduce carcinogenesis.

It is well-known that the expression of several enzymes is associated with detoxifying/antioxidant genes on the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway. Kelch-like ECH-associated protein 1 (Keap1) is a repressor protein that binds to Nrf2. Thus, the loss of interactions between Keap1 and Nrf2 proteins favors their dissociation and the subsequent nuclear translocation of Nrf2, while also transactivating the ARE in the promoter region of target genes (such as SOD, CAT, GPx, HO-1, and NQO1) and inhibiting ROS production.[85−87] Bhakkiyalakshmi and colleagues revealed that pterostilbene was able to activate the Nrf2/ARE pathway due to pterostilbene-favorable interactions with the arginine triad residues (R380, R415, R480) in the Keap1 kelch domainthus further activating Nrf2 by nuclear translocation as well as ARE-driven downstream target gene expression.[88] Pterostilbene treatment of colon HT-29 cells results in significantly increased GST and NQO1 activity as well as GSH levels.[81] In addition, pterostilbene was found to inhibit miR-377, leading to an increase in SOD expression and activity in fructose-induced conditionally immortalized mouse podocyte cell and Sprague−Dawley rat podocyte oxidative stress and injury models.[89]

Carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic (aromatic) amines (HCAs or HAAs) are ubiquitous in dietary and environmental systems. Members of the human cytochrome P450 family have important roles in the activation of a wide range of environmental procarcinogens.[90] Thus, a recent study postulated that selecting inhibitors of the cytochrome P450 family or another metabolizing enzyme could reduce the risk of mutagenesis and cancer. Mikstacka et al. reported that pterostilbene could inhibit CYP1A2 catalytic activities in a 7-ethoxyresorufin-*O*-deethylation (EROD) assay.[91] The authors further found that pterostilbene exhibited potent inhibitory activity toward CYP1A1 and CYP1B.[92] Moreover, research has shown that pterostilbene has the highest inhibitory effect toward CYP2C8 and UGT1A6 activity in *in vitro* assays.[93] These studies collectively demonstrate that pterostilbene may exert potential health benefits related to the inhibition of the initiation stage of carcinogenesis.

Chemopreventive Effects of Pterostilbene in Promotion Stage of Carcinogenesis. In the tumor promotion process, transformation to malignant cells is accelerated generally via oxidative stress and chronic inflammation. Furthermore, during this stage, the mutant cells begin their loss of regulated cell proliferation while simultaneously evading apoptosis and immune surveillance.[2,53]

Apoptosis, namely, programmed cell death or cellular suicide, has a critical role in maintaining the balance in multicellular organisms. It is particularly important in embryonic development, the shaping of organs, regulating the immune system, and eliminating potential cancer cells. Apoptosis requires multistep, multipathway, and highly ordered processes that terminate in the enzymatic breakdown of cellular DNA. Apoptosis can be initiated either through the mitochondria (intrinsic pathway) or death receptor ligation (extrinsic pathway).[94,95] Also, various environmental stresses, such as ROS, hypoxia, genotoxic compounds, and ER Ca^{2+} depletion, can perturb ER, induce unfolded protein accumulation, and then lead to ER stress, which can affect the P53 upregulated modulator of apoptosis (PUMA) or Bcl-2 protein families, which ultimately regulate apoptosis.[96] The mitochondrial pathway is controlled by the Bcl-2 protein family, which includes both pro-apoptotic and antiapoptotic members. It has been proven that pterostilbene can upregulate the expression of the pro-apoptotic factors Bax, Bad, Bak, and Bid; downregulate the antiapoptotic factors Bcl-2, Bcl-xl, and Mcl-1; and decrease the mitochondrial membrane potential. Subsequently, cytochrome C, Smac/DIABLO, and cytosol expression induces caspase activation (such as caspase 9 and caspase 3/7) directly, consequently resulting in programmed cell death. Conversely, Smac/DIABLO can allow apoptosis to proceed by blocking the inhibitor of the apoptosis proteins.[97−99] The death receptor ligation pathway is triggered by the death receptor Fas via the Fas ligand. Under these circumstances, downstream caspases are activated in the apoptosis cascade. It is found that pterostilbene increases Fas and Fas ligand expression. In addition, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis and can bind to four different receptors, DR4 and DR5 (two pro-apoptotic death receptors, or DRs) and DcR1 and DcR2 (two antiapoptotic decoy receptors, or DcRs). Research has suggested that pterostilbene induces cancer cell exogenous apoptosis, which, through increasing DR4/5 and decreasing DcR-1/2 expression, ultimately activates caspase 3/7/8.[7,100−102] Studies have reported that pterostilbene treatment enhances ER stress by upregulating the phospho- PKR-like ER kinase (p-PERK), activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) expressions, leading to ER Ca^{2+} depletion and cytoplasm-induced apoptosis in cancer cells.[103,104] Taken together, it is obvious that pterostilbene can augment apoptosis in cancer cells, giving it potential in cancer chemoprevention.[15]

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Autophagy is a mechanism that maintains cellular homeostasis by fusing with lysosomes to degrade aggregated proteins, damaged organelles, and other undesirable cytoplasmic materials in response to many different forms of stress. In specific conditions, autophagy improves survival during starvation or leads to programmed cell death. Nevertheless, the role of autophagy in human diseases is intricate and disputed. For instance, in tumors, autophagy may trigger cytoprotective mechanisms by degrading the cytotoxic substances for energy reuse. However, when a cell undergoes damage that is irreversible or results in stress overload, autophagy could play an important role as executioner.[105] Numerous recent studies have shown that pterostilbene induces both autophagy and apoptosis in several cancerous cells in which autophagy plays a more pro-death role than a pro-survival role.[106] Wang et al. have suggested that pterostilbene inhibits cell proliferation and causes S phase cell cycle arrest in human cholangiocarcinoma cells by inducing autophagy via p62 downregulation, thus leading to elevated expression of endogenous Beclin-1, autophagy related protein 5 (ATG5), and microtubule-associated protein 1A/1B-light chain 3-II (LC3-II), and increases in LC3-I.[107] The authors reveal that pterostilbene could induce autophagy, as evident by the increases of LC3-I and LC3-II, in addition to apoptosis and cell cycle arrest in Bcap-37 and MCF-7 breast cancer cell lines.[108] Similarly, Ko et al. report that pterostilbene inhibits the cell growth of SAS and OECM-1 human oral cancer cells by inducing cell cycle arrest and apoptosis. It also induced autophagy, as indicated by increases in Beclin-1, LC3-II, and LC3-I, through regulating the activation of JNK1/2 and the inhibition of Akt, ERK1/2, and p38.[109] Interestingly, pterostilbene inhibits hepatocellular carcinoma cell growth without the induction of apoptosis in an ER stress and autophagy-dependent p-eIF2α /ATF4/LC-3 pathway.[110] Furthermore, pterostilbene has been confirmed to induce autophagy in tumor cells, which in turn impacts one form of programmed cell death or inhibits tumor growth and malignant transformation. The induction of autophagy by pterostilbene seems to be a promising strategy for anticancer strategies. However, studies in this area remain insufficient, and the mechanism of pterostilbene in cancer autophagy warrants further exploration.

The most fundamental characteristic of a tumor is uncontrolled cell proliferation, and the loss of the regulation of the cell cycle is a critical factor. Thus, inducing cell cycle arrest in cancer cells might limit malignancy during carcinogenesis.[111] Several *in vivo* and *in vitro* studies have revealed that pterostilbene suppresses cancer cell proliferation via multiple pathways. It was reported that pterostilbene inhibited cell growth in the prostate cancer DU145 and 22Rv1cell lines by decreasing the expression of miR-17, miR-21a, and miR-106a/b, thus restoring phosphatase and tensin homologue (PTEN) tumor suppressor expression. In this study, pterostilbene also reduced tumor growth via the reduction in circulating miR-17-5p and miR-106a-5p levels as well as restoring PTEN level in the xenograft model.[112] The study demonstrated the PTEN can control the cell cycle via many pathways but likely through regulating the PI3K/AKT pathway.[113] Pterostilbene is found to downregulate the PI3K/Akt/mTOR signaling pathway induction of mantle cell lymphoma JeKo-1 and the Granta-519 cell line apoptosis and cell cycle arrest at the G0/G1 phase.[114] Additionally Chen et al. indicate that pterostilbene, via the inhibition of the EGFR/PI3K/Akt/ERK/mTOR signaling pathway, decreases urethane-induced lung tumorigenesis.[59] Moreover, a study has shown that pterostilbene can upregulate a cell-intrinsic checkpoint and repair response protein p53, p21, p27, and p16 expression as well as downregulate the cyclin-dependent kinase levels of cyclin A, cyclin E, Cdk2, Cdk4, and Cdk6, which are associated with Rb phosphorylation, resulting in HL-60 gastric carcinoma cell G1 arrest.[102] Tan et al. showed that pterostilbene-induced H520 lung squamous carcinoma cell S phase accumulation was accomplished via downregulated cyclin A and cyclin E as well as the upregulation of p21 and p27 expression.[115] Pterostilbene was also found to activate the ataxia telangiectasia mutated (ATM) and check point kinases 1/2 (CHK1/2) pathways upstream of p53, thus inhibiting NSCLC and A549 lung cancer cell proliferation.[116] Furthermore, research has demonstrated that pterostilbene decreases the levels of cyclin A2, CDK2, and cdc25A as well as upregulating the level of Chk2-induced accumulation of lymphoma cells in the S-phase.[117] In summary, pterostilbene can, through a series of signaling pathways, contribute dramatically to cell cycle arrest and suppress cancer promotion and progression.

Chemopreventive Effects of Pterostilbene in Progression Stage of Carcinogenesis. Approximately 90% of deaths of cancer patients occur during the progression stage in carcinogenesis. An ample supply of nutrients allows malignant cells to invade surrounding tissues, ultimately migrating from the primary tumor to distant organs and proliferating at metastatic sites.[118] Pterostilbene has been reported to aid against angiogenesis and suppress cancer invasion and metastasis.

Angiogenesis is indispensable for invasive tumor growth and metastasis since it makes possible the extensive vascular network needed to deliver oxygen and nutrients to, as well as remove metabolic wastes from, tumors. Thus, regulating tumor-associated angiogenesis is a chemotherapeutic strategy used to limit cancer progression. Many cytokines (inflammatory microenvironment) and antiangiogenic factors regulate the process of angiogenesis, for which the most important positive regulatory factor is VEGF. Substantial evidence suggests that pterostilbene can suppress angiogenesis. A study has revealed that pterostilbene decreases VEGF production in SK-MEL-2 human melanoma cell lines.[119] It has been found that pterostilbene significantly suppressed AOM-induced GSK3 β phosphorylation and Wnt/β-catenin signaling, resulting in VEGF inhibition in ICR mice.[78] Moreover, pterostilbene reduces the MTA1-associated proangiogenic factors HIF-1α, VEGF, and IL-1β, leading to decreased angiogenesis in PC3M prostate cancer cells.[120] Also, Dhar et al. report that pterostilbene inhibition of MTA1 led to decreased hemangiogenesis and lymhangiogenesis, as evinced by CD31, VEGF-C, and IL-1β immunostaining and immunoblot analyses in Pten$^{+/f}$ prostate-specific heterozygous mice.[121] Similarly, Li et al. found that pterostilbene inhibited MTA1 *in vivo* and decreased angiogenesis.[122] In addition, pterostilbene suppresses angiogenesis by targeting c-Met, whose inactivation decreases perivascular migration, invasion, and angiogenesis through IL-8 and CXCL1-mediated CXCR1 signaling in breast carcinoma 231BrM cells.[123]

Tumor cell invasion and metastasis are modulated by several microenvironmental factors such as matrix metalloproteinases (MMPs), EGFs, and extracellular matrixes (ECMs). In the MDA-MB-231 human breast cancer cell line, pterostilbene decreases tumor cell migration and invasion caused by

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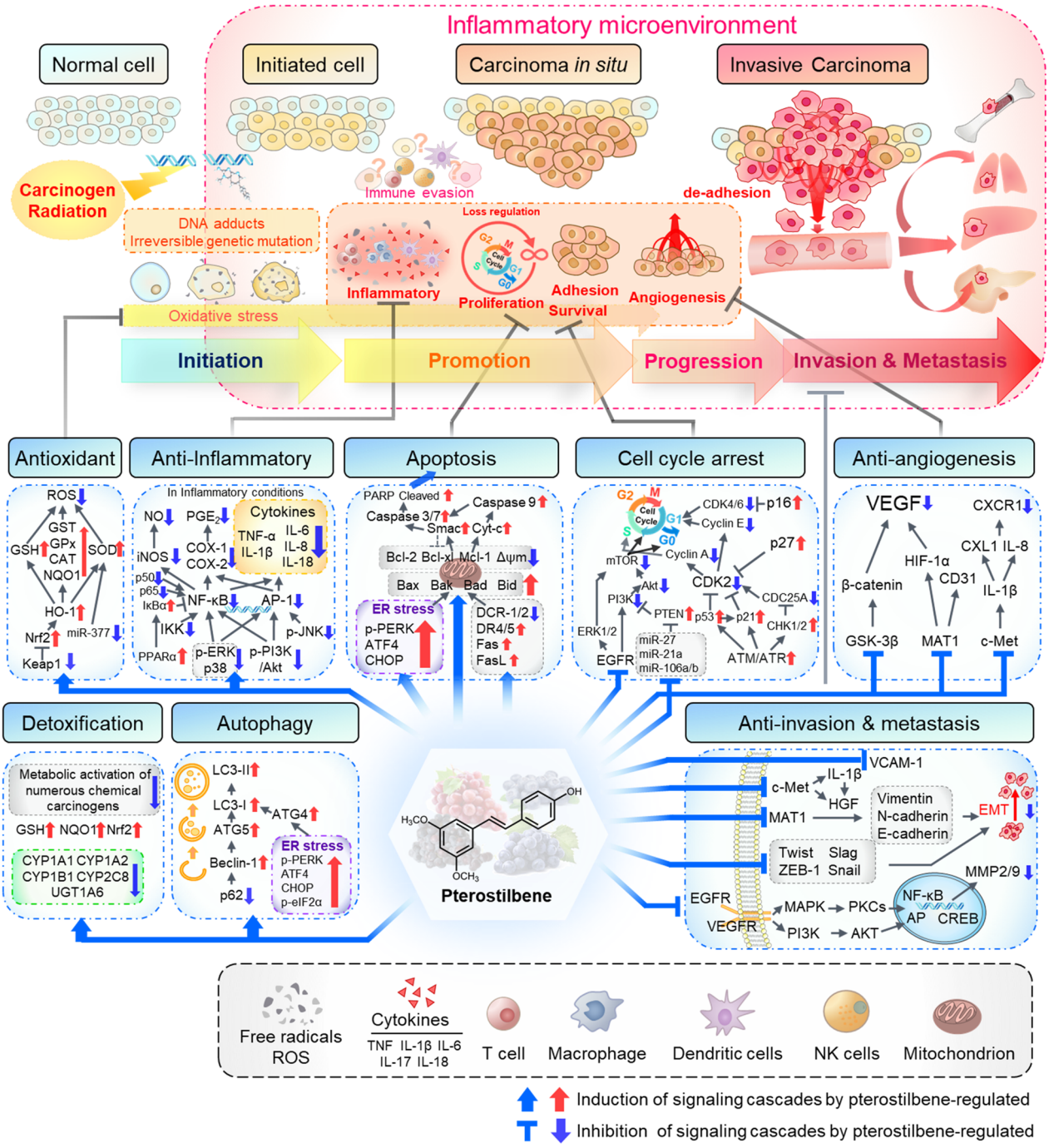

Figure 3. Schematic representation of the chemopreventive effects of pterostilbene on the multiple stages of carcinogenesis. Pterostilbene could markedly inhibit the carcinogenesis via modulation of multiple signaling pathways, including induction of detoxification and antioxidant enzymes, antiproliferation and cell cycle arrest, induction of apoptosis as well as the regulation of autophagy, inhibition of invasion and metastasis, antiangiogenesis.

invadopodium formation by suppressing the expression of constitutively active c-Src, cortactin, Tks5, MT1-MMP, Twist1, and PDGFR-α as well as decreasing the activity of MMP-2/9.[124] Moreover, pterostilbene has been shown to, via downregulated PKC, EGF, and VEGF, then through blocking the phosphorylation of MAPK and PI3K/AKT pathway, inhibit NFκB and AP-1 activity, thereby suppressing MMP-9 gene expression against TPA-mediated HepG 2 cell line metastasis.[125] Likewise, research has demonstrated that pterostilbene can inhibit CREB, NFκB, and SP-1 expression as well as DNA-binding activities on MMP-2 and u-PA promoters, reduce MMP-2 and u-PA expression, and subsequently inhibit the effects on oral cancer SCC-9 cell line invasion and migration.[126] An epithelial-mesenchymal transition (EMT) is a salient preliminary step in metastasis that allows cancer cells to acquire migratory and invasive abilities.[127] Su and colleagues reveal that pterostilbene can upregulate E-cadherin and downregulate the EMT markers Snail, Slug, vimentin, and ZEB1 expression, thus inhibiting triple-negative MDA-MB-231 and Hs578t breast cancer cells as well as the MDA-MB-231 cell tumor xenograft model migration and invasion.[128] Also, pterostilbene can suppress

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EMT status by decreasing NFκB, Twist1, and vimentin as well as increasing the E-cadherin level in both M2 TAM-cocultured MCF7 and MDA-MB-231 cells as well as the MDA-MB-231 cell xenograft model.[129] Additionally, pterostilbene can reduce EMT and migration by upregulating E-Cadherin and downregulating N-Cadherin, Twist, Snail, Slug, vimentin, ZEB1, and ZEB2 expression in MCF7 breast cancer cells.[130] Moreover, pterostilbene decreases MTA1 protein levels, resulting in the downregulation of EMT-related tumor metastasis factor vimentin as well as the upregulation of E-cadherin in prostate-specific Pten $^{f/f}$ mouse models.[121] Similarly, research shows that pterostilbene inhibits MTA1 in prostate cancer.[121,122] In addition, pterostilbene suppresses vascular adhesion molecule 1 (VCAM-1) expression in the hepatic sinusoidal endothelium, which decreases B16M-F10 cell adhesion to the endothelium.[131] These findings suggest that pterostilbene possesses antiangiogenesis and anti-invasion/metastasis properties because it regulates multiple signaling molecules.

Combinatorial Strategies of Pterostilbene with Phytochemicals for Cancer Chemoprevention. The stratagem of using a combination of dietary phytochemicals with drug therapies has shown many advantages, for instance, decreasing side effects and dosage, preventing drug resistance, and increasing patient tolerance which also strengthens pharmacological actions. Many studies demonstrate that pterostilbene cotreatment with drugs has the potential to inhibit or delay carcinogenesis. For example, pterostilbene and 5-fluorouracil cotreatment showed potent anticancer effects in Caco-2 colon cancer cells. In MCF7 and ZR-75-1 breast cancer cells, higher efficacy of cell viability reduction was observed with pterostilbene and tamoxifen cotreatment.[15,132,133] Integrative oncology is a new focus in cancer research, with treatment that focuses on natural phytochemicals as nontoxic tools that can cooperate with current cancer therapies in the hope they can enhance the efficacy of traditional treatments. Several research studies have shown that the combination of pterostilbene with phytochemicals could be a potential strategy for chemotherapy of cancer. Pterostilbene and (−)-epigallocatechin-3-gallate cotreatment in both pancreatic cancer MIA PaCa-2 and PANC-1 cell inhibits cell growth and induces apoptosis through the mitogen-activated protein kinase pathways.[134] Moreover, pterostilbene cotreatment with 6-shogaol increases the anticancer activity of paclitaxel in MCF-7 breast cancer cells.[135] Singh et al. showed that a combination of pterostilbene and lupeol was more effective in reducing tumorigenesis and ROS generation in B[a]P-induced mouse skin carcinogenesis.[136] The combination of pterostilbene and astragalus enhances apoptosis and inhibits the cell growth of melanoma in SK-MEL-2 cells and in SK-MEL-2 bearing mice.[137] Pterostilbene combined with curcumin demonstrated significant potency to decrease LOX-mediated activity, thus suppressing HCC cell metastasis induced by long-term ethanol exposure.[138] Taken together, these findings suggest that pterostilbene cotreatment with other phytochemicals brings synergy benefits or targets multiple molecular mechanisms to boost the efficacy of anticancer treatments. Further investigation and validation in the form of more clinical studies and applications are warranted.

Overall, pterostilbene, the 3,5-dimethoxy motif at the A-phenyl ring of resveratrol has increased bioavailability with preserved beneficial activity. Pterostilbene exerts potent anticancer actions through its regulation of multiple cell signaling pathways and has multiple direct and/or indirect targets within cells. These signals interact to diminish the risk of carcinogenesis (initiation, promotion, and progression stages). These mechanisms include the induction of detoxification and antioxidant enzymes, anti-inflammation actions, the arrest of cell-cycle progression, and pro-apoptotic as well as the regulation of autophagy, antiangiogenesis, anti-invasion activities, and metastasis (Figure 3). Based on the portion *in vivo* study,[15,78,139] conversion of animal doses to human equivalent doses, the dietary intake of approximately 192−1200 mg/day in 60 kg human can be suggested. Nevertheless, the evidence as to whether pterostilbene can mediate immune surveillance, which regulates the relation between the autophagy and apoptosis mechanisms, is still lacking. Moreover, clear solubility, stability, and clinical trials for pterostilbene are still needed in order to develop it into a chemopreventive and chemotherapeutic agent.

AUTHOR INFORMATION

Corresponding Authors

Min-Hsiung Pan − *Institute of Food Science and Technology, National Taiwan University, Taipei 10617, Taiwan; Department of Medical Research, China Medical University Hospital, China Medical University, Taichung 40402, Taiwan; Department of Health and Nutrition Biotechnology, Asia University, Taichung 41354, Taiwan;* orcid.org/0000-0002-5188-7030; Phone: +886-2-33664133; Email: mhpan@ntu.edu.tw; Fax: +886-2-33661771

Chi-Tang Ho − *Department of Food Science, Rutgers University, New Brunswick, New Jersey 08901-8520, United States;* orcid.org/0000-0001-8273-2085; Phone: +1-848-932-5553; Email: ho@aesop.rutgers.edu; Fax: +1-732-932-6776

Authors

Wei-Sheng Lin − *Institute of Food Science and Technology, National Taiwan University, Taipei 10617, Taiwan*

Jane Valorie Leland − *Leland Global Enterprises, LLC, Wilmette, Illinois 60091, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jafc.9b07860

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ABBREVIATIONS USED

Akt, protein kinase B; AOM, azoxymethane; AP-1, activator protein 1; ARE, antioxidant response element; ATF4, activating transcription factor 4; ATG, autophagy related protein; 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-2, B-cell lymphoma-2; Bcl-xl, bcl-X Protein; Bid, BH3 interacting domain death agonist

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protein; CAT, catalase; CD31, cluster of differentiation 31; CDC25A, cell division cycle protein A; CDK, cyclin-dependent kinase; CHK, check point kinases; CHOP, C/EBP homologous protein; c-Met, mesenchymal-epithelial transition factor; COX, cyclooxygenase; CREB, AMP response element binding protein; CXCL1, chemokine (C-X-C motif) ligand 1; CXCR1, interleukin (IL)-8/C-X-C chemokine receptor 1; CYP, cytochrome enzyme; Cyt-c, cytochrome c; DCR1/2, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors 3/4; DIABLO, Diablo homologue; DR4/5, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors 1/2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; eIF2, eukaryotic initiation factor 2; EMT, epithelial-mesenchymal transition; ER stress, endoplasmic reticulum stress; ERK, extracellular signal-regulated protein kinase; ERK, extracellular signal-regulated protein kinase; ERK1/2, extracellular signal regulated kinases 1/2; Fas, factor associated suicide; FasL, factor associated suicide ligand; GPx, glutathione peroxidase; GSK-3β, glycogen synthase kinase-3; GST, glutathione-S-transferase; HGF, hepatocyte-growth factor; HIF-1α, hypoxic response transcription factor-1α; HO-1, heoxygenase-1; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IKK, I kappa B kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, jun amino-terminal kinase; Keap1, kelch-like ECH-associated protein 1; LC3, microtubule-associated protein 1A/1B-light chain 3; MAPK, mitogen-activated protein kinase; Mcl-1, myeloid cell leukemia-1; MMPs, matrix metalloproteinases; MTA1, metastasis-associated protein 1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NK cells, natural killer cells; NO, nitric oxide; NQO1, NAD(P)H:quinone oxidoreductase1; Nrf2, nuclear factor erythroid 2-related factor 2; p62, autophagic receptor p62; p65, nuclear factor NF-kappa-B p65 subunit; PERK, PKR-like ER kinase; PGE2, prostaglandin E2; PI3K, phosphatidylinositol-3-kinase; PKC, protein kinase C; PPARα, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homologue; PUMA, P53 upregulated modulator of apoptosis; ROS, reactive oxygen species; Smac, second mitochondria-derived activator of caspase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; UDP, Uridine 5′-diphospho; UGT1A6, UDP-glucuronosyltransferase 1-6; VCAM, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor; $\Delta\Psi$ m, mitochondrial membrane potential

REFERENCES

(1) Moolgavkar, S. H. Model for human carcinogenesis: action of environmental agents. *Environ. Health Perspect.* **1983**, *50*, 285−291.

(2) Hanahan, D.; Weinberg, R. A. The hallmarks of cancer. *Cell* **2000**, *100* (1), 57−70.

(3) Grivennikov, S. I.; Greten, F. R.; Karin, M. Immunity, inflammation, and cancer. *Cell* **2010**, *140* (6), 883−899.

(4) Clevers, H. At the crossroads of inflammation and cancer. *Cell* **2004**, *118*, 671−674.

(5) Surh, Y. J. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer* **2003**, *3* (10), 768−780.

(6) Greenwald, P. Cancer Chemoprevention. *BMJ* **2002**, *324*, 714−718.

(7) Kosuru, R.; Rai, U.; Prakash, S.; Singh, A.; Singh, S. Promising therapeutic potential of pterostilbene and its mechanistic insight based on preclinical evidence. *Eur. J. Pharmacol.* **2016**, *789*, 229−243.

(8) Etxeberria, U.; Hijona, E.; Aguirre, L.; Milagro, F. I.; Bujanda, L.; Rimando, A. M.; Martinez, J. A.; Portillo, M. P. Pterostilbene-induced changes in gut microbiota composition in relation to obesity. *Mol. Nutr. Food Res.* **2017**, *61* (1), 1500906.

(9) Aguirre, L.; Milton-Laskibar, I.; Hijona, E.; Bujanda, L.; Rimando, A. M.; Portillo, M. P. Effects of pterostilbene in brown adipose tissue from obese rats. *J. Physiol. Biochem.* **2016**, *73* (3), 457−464.

(10) Gomez-Zorita, S.; Belles, C.; Briot, A.; Fernandez-Quintela, A.; Portillo, M. P.; Carpene, C. Pterostilbene inhibits lipogenic activity similar to resveratrol or caffeine but differently modulates lipolysis in adipocytes. *Phytother. Res.* **2017**, *31* (8), 1273−1282.

(11) La Spina, M.; Galletta, E.; Azzolini, M.; Gomez Zorita, S.; Parrasia, S.; Salvalaio, M.; Salmaso, A.; Biasutto, L. Browning effects of a chronic pterostilbene supplementation in mice fed a high-fat diet. *Int. J. Mol. Sci.* **2019**, *20* (21), 5377.

(12) Gomez-Zorita, S.; Fernandez-Quintela, A.; Lasa, A.; Aguirre, L.; Rimando, A. M.; Portillo, M. P. Pterostilbene, a dimethyl ether derivative of resveratrol, reduces fat accumulation in rats fed an obesogenic diet. *J. Agric. Food Chem.* **2014**, *62* (33), 8371−8378.

(13) Trepiana, J.; Gomez-Zorita, S.; Fernandez-Quintela, A.; Gonzalez, M.; Portillo, M. P. Effects of resveratrol and its analogue pterostilbene, on NOV/CCN3 adipokine in adipose tissue from rats fed a high-fat high-sucrose diet. *J. Physiol. Biochem.* **2019**, *75* (3), 275−283.

(14) McCormack, D.; McFadden, D. Pterostilbene and cancer: Current review. *J. Surg. Res.* **2012**, *173* (2), No. e53.

(15) Ma, Z.; Zhang, X.; Xu, L.; Liu, D.; Di, S.; Li, W.; Zhang, J.; Zhang, H.; Li, X.; Han, J.; Yan, A. Pterostilbene: Mechanisms of its action as oncostatic agent in cell models and in vivo studies. *Pharmacol. Res.* **2019**, *145*, 104265.

(16) Fulda, S. Resveratrol and derivatives for the prevention and treatment of cancer. *Drug Discovery Today* **2010**, *15* (17−18), 757−765.

(17) Rodriguez-Bonilla, P.; Mendez-Cazorla, L.; Lopez-Nicolas, J. M.; Garcia-Carmona, F. Kinetic mechanism and product characterization of the enzymatic peroxidation of pterostilbene as model of the detoxification process of stilbene-type phytoalexins. *Phytochemistry* **2011**, *72*, 100−108.

(18) Kapetanovic, I. M.; Muzzio, M.; Huang, Z.; Thompson, T. N.; McCormick, D. L. Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. *Cancer Chemother. Pharmacol.* **2011**, *68* (3), 593−601.

(19) Lin, H. S.; Yue, B. D.; Ho, P. C. Determination of pterostilbene in rat plasma by a simple HPLC-UV method and its application in pre-clinical pharmacokinetic study. *Biomed. Chromatogr.* **2009**, *23* (12), 1308−1315.

(20) Wang, P.; Sang, S. Metabolism and pharmacokinetics of resveratrol and pterostilbene. *BioFactors* **2018**, *44* (1), 16−25.

(21) Ruiz, M. J.; Fernandez, M.; Pico, Y.; Manes, J.; Asensi, M.; Carda, C.; Asensio, G.; Estrela, J. M. Dietary administration of high doses of pterostilbene and quercetin to mice is not toxic. *J. Agric. Food Chem.* **2009**, *57* (8), 3180−3186.

(22) Riche, D. M.; McEwen, C. L.; Riche, K. D.; Sherman, J. J.; Wofford, M. R.; Deschamp, D.; Griswold, M. Analysis of safety from a human clinical trial with pterostilbene. *J. Toxicol.* **2013**, *2013*, 1.

(23) Pezet, R.; Pont, V. Ultrastructural Observations of Pterostilbene Fungitoxicity in Dormant Conidia of Botrytis cinerea Pers. *J. Phytopathol.* **1990**, *129* (1), 19−30.

(24) Langcake, P. Disease resistance of Vitis spp. and the production of the stress metabolites resveratrol, ε-viniferin, α-viniferin and pterostilbene. *Physiol. Plant Pathol.* **1981**, *18* (2), 213−226.

(25) Adrian, M.; Jeandet, P.; Douillet-Breuil, A. C.; Tesson, L.; Bessis, R. Stilbene content of mature Vitis vinifera berries in response to UV-C elicitation. *J. Agric. Food Chem.* **2000**, *48* (12), 6103−6105.

(26) Seshadri, T. R. Polyphenols of Pterocarpus and Dalbergia woods. *Phytochemistry* **1972**, *11* (3), 881−898.

(27) Schmidlin, L.; Poutaraud, A.; Claudel, P.; Mestre, P.; Prado, E.; Santos-Rosa, M.; Wiedemann-Merdinoglu, S.; Karst, F.; Merdinoglu, D.; Hugueney, P. A stress-inducible resveratrol O-methyltransferase

https://dx.doi.org/10.1021/acs.jafc.9b07860
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

involved in the biosynthesis of pterostilbene in grapevine. *Plant Physiol.* **2008**, *148* (3), 1630−1639.
(28) Langcake, P.; Pryce, R. J. A new class of phytoalexins from grapevines. *Experientia* **1977**, *33*, 151−152.
(29) Rimando, A. M.; Kalt, W.; Magee, J. B.; Dewey, J.; Ballington, J. R. Resveratrol, pterostilbene, and piceatannol in Vaccinium berries. *J. Agric. Food Chem.* **2004**, *52* (15), 4713−4719.
(30) Pezet, R.; Pont, V. Mise en évidence de ptérostilbène dans les grappes de Vitis vinifera. *Plant Physiol. Biochem.* **1988**, *26*, 603−607.
(31) Martínez-Márquez, A.; Morante-Carriel, J. A.; Ramírez-Estrada, K.; Cusidó, R. M.; Palazon, J.; Bru-Martínez, R. Production of highly bioactive resveratrol analogues pterostilbene and piceatannol in metabolically engineered grapevine cell cultures. *Plant Biotechnol. J.* **2016**, *14* (9), 1813−1825.
(32) Miltonprabu, S. Quercetin: A flavonol with versatile therapeutic applications and its interactions with other drugs. *Nonvitamin Nonmineral Nutr. Suppl.* **2019**, 75−83.
(33) Ting, Y.; Zhao, Q.; Xia, C.; Huang, Q. Using in vitro and in vivo models to evaluate the oral bioavailability of nutraceuticals. *J. Agric. Food Chem.* **2015**, *63* (5), 1332−1338.
(34) Hebert, M. F. Impact of pregnancy on maternal pharmacokinetics of medications. *J. Popul. Ther. Clin. Pharmacol.* **2013**, *20*, 17−39.
(35) Wen, X.; Walle, T. Methylated flavonoids have greatly improved intestinal absorption and metabolic stability. *Drug Metab. Dispos.* **2006**, *34* (10), 1786−1792.
(36) Akinwumi, B. C.; Bordun, K.-A. M.; Anderson, H. D. Biological activities of stilbenoids. *Int. J. Mol. Sci.* **2018**, *19* (3), 792.
(37) Aires, V.; Delmas, D.; Le Bachelier, C.; Latruffe, N.; Schlemmer, D.; Benoist, J.-F.; Djouadi, F.; Bastin, J. Stilbenes and resveratrol metabolites improve mitochondrial fatty acid oxidation defects in human fibroblasts. *Orphanet J. Rare Dis.* **2014**, *9*, 79−79.
(38) Aires, V.; Limagne, E.; Cotte, A. K.; Latruffe, N.; Ghiringhelli, F.; Delmas, D. Resveratrol metabolites inhibit human metastatic colon cancer cells progression and synergize with chemotherapeutic drugs to induce cell death. *Mol. Nutr. Food Res.* **2013**, *57* (7), 1170−1181.
(39) Eseberri, I.; Lasa, A.; Churruca, I.; Portillo, M. P. Resveratrol metabolites modify adipokine expression and secretion in 3T3-L1 preadipocytes and mature adipocytes. *PLoS One* **2013**, *8* (5), No. e63918.
(40) Lasa, A.; Churruca, I.; Eseberri, I.; Andres-Lacueva, C.; Portillo, M. P. Delipidating effect of resveratrol metabolites in 3T3-L1 adipocytes. *Mol. Nutr. Food Res.* **2012**, *56* (10), 1559−1568.
(41) Shao, X.; Chen, X.; Badmaev, V.; Ho, C. T.; Sang, S. Structural identification of mouse urinary metabolites of pterostilbene using liquid chromatography/tandem mass spectrometry. *Rapid Commun. Mass Spectrom.* **2010**, *24* (12), 1770−1778.
(42) Storniolo, C. E.; Moreno, J. J. Resveratrol analogs with antioxidant activity inhibit intestinal epithelial cancer Caco-2 cell growth by modulating arachidonic acid cascade. *J. Agric. Food Chem.* **2019**, *67* (3), 819−828.
(43) Lelakova, V.; Smejkal, K.; Jakubczyk, K.; Vesely, O.; Landa, P.; Vaclavik, J.; Bobal, P.; Pizova, H.; Temml, V.; Steinacher, T.; Schuster, D.; Granica, S.; Hanakova, Z.; Hosek, J. Parallel in vitro and in silico investigations into anti-inflammatory effects of non-prenylated stilbenoids. *Food Chem.* **2019**, *285*, 431−440.
(44) van den Brand, A. D.; Villevoye, J.; Nijmeijer, S. M.; van den Berg, M.; van Duursen, M. B. M. Anti-tumor properties of methoxylated analogues of resveratrol in malignant MCF-7 but not in non-tumorigenic MCF-10A mammary epithelial cell lines. *Toxicology* **2019**, *422*, 35−43.
(45) Sun, Y.; Wu, X.; Cai, X.; Song, M.; Zheng, J.; Pan, C.; Qiu, P.; Zhang, L.; Zhou, S.; Tang, Z.; Xiao, H. Identification of pinostilbene as a major colonic metabolite of pterostilbene and its inhibitory effects on colon cancer cells. *Mol. Nutr. Food Res.* **2016**, *60* (9), 1924−1932.
(46) Hsieh, M. J.; Chin, M. C.; Lin, C. C.; His, Y. T.; Lo, Y. S.; Chuang, Y. C.; Chen, M. K. Pinostilbene hydrate suppresses human oral cancer cell metastasis by downregulation of Matrix Metalloproteinase-2 through the Mitogen-Activated Protein Kinase signaling pathway. *Cell. Physiol. Biochem.* **2018**, *50* (3), 911−923.
(47) Allen, E. N.; Potdar, S.; Tapias, V.; Parmar, M.; Mizuno, C. S.; Rimando, A.; Cavanaugh, J. E. Resveratrol and pinostilbene confer neuroprotection against aging-related deficits through an ERK1/2-dependent mechanism. *J. Nutr. Biochem.* **2018**, *54*, 77−86.
(48) Tsai, H.-Y.; Ho, C.-T.; Chen, Y.-K. Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. *J. Food Drug Anal.* **2017**, *25* (1), 134−147.
(49) Tolomeo, M.; Grimaudo, S.; Cristina, A. D.; Roberti, M.; Pizzirani, D.; Meli, M.; Dusonchet, L.; Gebbia, N.; Abbadessa, V.; Crosta, L.; Barucchello, R.; Grisolia, G.; Invidiata, F.; Simoni, D. Pterostilbene and 3′-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells. *Int. J. Biochem. Cell Biol.* **2005**, *37* (8), 1709−1726.
(50) Lai, C. S.; Yang, G.; Li, S.; Lee, P. S.; Wang, B. N.; Chung, M. C.; Nagabhushanam, K.; Ho, C. T.; Pan, M. H. 3′-Hydroxypterostilbene suppresses colitis-associated tumorigenesis by inhibition of IL-6/STAT3 signaling in mice. *J. Agric. Food Chem.* **2017**, *65* (44), 9655−9664.
(51) Cheng, T. C.; Lai, C. S.; Chung, M. C.; Kalyanam, N.; Majeed, M.; Ho, C. T.; Ho, Y. S.; Pan, M. H. Potent anti-cancer effect of 3′-hydroxypterostilbene in human colon xenograft tumors. *PLoS One* **2014**, *9* (11), No. e111814.
(52) Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **2008**, *454* (7203), 428−435.
(53) Mantovani, A.; Allavena, P.; Sica, A.; Balkwill, F. Cancer-related inflammation. *Nature* **2008**, *454* (7203), 436−444.
(54) Li, J.; Ruzhi Deng; Hua, X.; Zhang, L.; Lu, F.; Coursey, T. G.; Pflugfelder, S. C.; Li, D.-Q. Blueberry component pterostilbene protects corneal epithelial cells from inflammation via anti-oxidative pathway. *Sci. Rep.* **2016**, *6*, 19408.
(55) Dvorakova, M.; Landa, P. Anti-inflammatory activity of natural stilbenoids: A review. *Pharmacol. Res.* **2017**, *124*, 126−145.
(56) Pan, M. H.; Wu, J. C.; Ho, C. T.; Lai, C. S. Antiobesity molecular mechanisms of action: Resveratrol and pterostilbene. *BioFactors (Oxford, England)* **2018**, *44*, 50−60.
(57) McCormack, D.; McFadden, D. A review of pterostilbene antioxidant activity and disease modification. *Oxid. Med. Cell. Longevity* **2013**, *2013*, 575482.
(58) Poulose, S. M.; Thangthaeng, N.; Miller, M. G.; Shukitt-Hale, B. Effects of pterostilbene and resveratrol on brain and behavior. *Neurochem. Int.* **2015**, *89*, 227−233.
(59) Chen, R. J.; Tsai, S. J.; Ho, C. T.; Pan, M. H.; Ho, Y. S.; Wu, C. H.; Wang, Y. J. Chemopreventive effects of pterostilbene on urethane-induced lung carcinogenesis in mice via the inhibition of EGFR-mediated pathways and the induction of apoptosis and autophagy. *J. Agric. Food Chem.* **2012**, *60* (48), 11533−11541.
(60) Ren, G.; Rimando, A. M.; Mathews, S. T. AMPK activation by pterostilbene contributes to suppression of hepatic gluconeogenic gene expression and glucose production in H4IIE cells. *Biochem. Biophys. Res. Commun.* **2018**, *498* (3), 640−645.
(61) Rimando, A. M.; Nagmani, R.; Feller, D. R.; Yokoyama, W. Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor α-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *J. Agric. Food Chem.* **2005**, *53* (9), 3403−3407.
(62) Delerive, P.; Gervois, P.; Fruchart, J. C.; Staels, B. Induction of Ikappa Balpha expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor-alpha activators. *J. Biol. Chem.* **2000**, *275* (47), 36703−36707.
(63) Lo Verme, J.; Fu, J.; Astarita, G.; La Rana, G.; Russo, R.; Calignano, A.; Piomelli, D. The nuclear receptor peroxisome proliferator-activated receptor-α mediates the anti-inflammatory actions of palmitoylethanolamide. *Mol. Pharmacol.* **2005**, *67* (1), 15−19.
(64) Hou, Y.; Xie, G.; Miao, F.; Ding, L.; Mou, Y.; Wang, L.; Su, G.; Chen, G.; Yang, J.; Wu, C. Pterostilbene attenuates lipopolysaccharide-induced learning and memory impairment possibly via inhibiting

https://dx.doi.org/10.1021/acs.jafc.9b07860
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

microglia activation and protecting neuronal injury in mice. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2014**, *54*, 92−102.
(65) Hou, Y.; Li, N.; Xie, G.; Wang, J.; Yuan, Q.; Jia, C.; Liu, X.; Li, G.; Tang, Y.; Wang, B. Pterostilbene exerts anti-neuroinflammatory effect on lipopolysaccharide-activated microglia via inhibition of MAPK signalling pathways. *J. Funct. Foods* **2015**, *19*, 676−687.
(66) Paul, S.; Rimando, A. M.; Lee, H. J.; Ji, Y.; Reddy, B. S.; Suh, N. Anti-inflammatory action of pterostilbene is mediated through the p38 mitogen-activated protein kinase pathway in colon cancer cells. *Cancer Prev. Res.* **2009**, *2* (7), 650−657.
(67) Zhang, L.; Zhou, G. Z.; Song, W.; Tan, X. R.; Guo, Y. Q.; Zhou, B.; Jing, H.; Zhao, S. J.; Chen, L. K. Pterostilbene protects vascular endothelial cells against oxidized low-density lipoprotein-induced apoptosis in vitro and in vivo. *Apoptosis* **2012**, *17* (1), 25−36.
(68) Choo, Q. Y.; Yeo, S. C. M.; Ho, P. C.; Tanaka, Y.; Lin, H.-S. Pterostilbene surpassed resveratrol for anti-inflammatory application: Potency consideration and pharmacokinetics perspective. *J. Funct. Foods* **2014**, *11*, 352−362.
(69) Carey, A. N.; Fisher, D. R.; Rimando, A. M.; Gomes, S. M.; Bielinski, D. F.; Shukitt-Hale, B. Stilbenes and anthocyanins reduce stress signaling in BV-2 mouse microglia. *J. Agric. Food Chem.* **2013**, *61* (25), 5979−5986.
(70) Pan, M.-H.; Chang, Y.-H.; Tsai, M.-L.; Lai, C.-S.; Ho, S.-Y.; Badmaev, V.; Ho, C.-T. Pterostilbene suppressed lipopolysaccharide-induced up-expression of INOS and COX-2 in murine macrophages. *J. Agric. Food Chem.* **2008**, *56* (16), 7502−7509.
(71) Wu, J.; Li, M.; He, J.; Lv, K.; Wang, M.; Guan, W.; Liu, J.; Tao, Y.; Li, S.; Ho, C.-T.; Zhao, H. Protective effect of pterostilbene on concanavalin A-induced acute liver injury. *Food Funct.* **2019**, *10* (11), 7308−7314.
(72) Lin, Y. J.; Ding, Y.; Wu, J.; Ning, B. T. Pterostilbene as treatment for severe acute pancreatitis. *GMR, Genet. Mol. Res.* **2016**, *15* (3), 15038330.
(73) Liu, H.; Wu, X.; Luo, J.; Wang, X.; Guo, H.; Feng, D.; Zhao, L.; Bai, H.; Song, M.; Liu, X.; Guo, W.; Li, X.; Yue, L.; Wang, B.; Qu, Y. Pterostilbene attenuates astrocytic inflammation and neuronal oxidative injury after ischemia-reperfusion by inhibiting NF-kappaB phosphorylation. *Front. Immunol.* **2019**, *10*, 2408.
(74) Cichocki, M.; Paluszczak, J.; Szaefer, H.; Piechowiak, A.; Rimando, A. M.; Baer-Dubowska, W. Pterostilbene is equally potent as resveratrol in inhibiting 12-O-tetradecanoylphorbol-13-acetate activated NFkappaB, AP-1, COX-2, and iNOS in mouse epidermis. *Mol. Nutr. Food Res.* **2008**, *52* (Suppl 1), S62−S70.
(75) Chiou, Y. S.; Tsai, M. L.; Nagabhushanam, K.; Wang, Y. J.; Wu, C. H.; Ho, C. T.; Pan, M. H. Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. *J. Agric. Food Chem.* **2011**, *59* (6), 2725−2733.
(76) Kutil, Z.; Kvasnicova, M.; Temml, V.; Schuster, D.; Marsik, P.; Cusimamani, E. F.; Lou, J. D.; Vanek, T.; Landa, P. Effect of dietary stilbenes on 5-lipoxygenase and cyclooxygenases activities in vitro. *Int. J. Food Prop.* **2015**, *18* (7), 1471−1477.
(77) Nikhil, K.; Sharan, S.; Palla, S. R.; Sondhi, S. M.; Peddinti, R. K.; Roy, P. Understanding the mode of action of a pterostilbene derivative as anti-inflammatory agent. *Int. Immunopharmacol.* **2015**, *28* (1), 10−21.
(78) Chiou, Y. S.; Tsai, M. L.; Wang, Y. J.; Cheng, A. C.; Lai, W. M.; Badmaev, V.; Ho, C. T.; Pan, M. H. Pterostilbene inhibits colorectal aberrant crypt foci (ACF) and colon carcinogenesis via suppression of multiple signal transduction pathways in azoxymethane-treated mice. *J. Agric. Food Chem.* **2010**, *58* (15), 8833−8841.
(79) Tsai, M. L.; Lai, C. S.; Chang, Y. H.; Chen, W. J.; Ho, C. T.; Pan, M. H. Pterostilbene, a natural analogue of resveratrol, potently inhibits 7,12-dimethylbenz[a]anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse skin carcinogenesis. *Food Funct.* **2012**, *3* (11), 1185−1194.
(80) Suh, N.; Paul, S.; Hao, X.; Simi, B.; Xiao, H.; Rimando, A. M.; Reddy, B. S. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. *Clin. Cancer Res.* **2007**, *13* (1), 350−355.
(81) Liu, J.; Fan, C.; Yu, L.; Yang, Y.; Jiang, S.; Ma, Z.; Hu, W.; Li, T.; Yang, Z.; Tian, T.; Duan, W.; Yu, S. Pterostilbene exerts an anti-inflammatory effect via regulating endoplasmic reticulum stress in endothelial cells. *Cytokine+* **2016**, *77*, 88−97.
(82) Wang, B.; Chiu, H.; Lee, Y.; Li, C.; Wang, Y.; Lee, Y. Pterostilbene Attenuates hexavalent chromium-induced allergic contact dermatitis by preventing cell apoptosis and inhibiting IL-β-related NLRP3 inflammasome activation. *J. Clin. Med.* **2018**, *7* (12), 489.
(83) Lin, B. W.; Gong, C. C.; Song, H. F.; Cui, Y. Y. Effects of anthocyanins on the prevention and treatment of cancer. *Br. J. Pharmacol.* **2017**, *174* (11), 1226−1243.
(84) Liu, Y.; Yin, T.; Feng, Y.; Cona, M. M.; Huang, G.; Liu, J.; Song, S.; Jiang, Y.; Xia, Q.; Swinnen, J. V.; Bormans, G.; Himmelreich, U.; Oyen, R.; Ni, Y. Mammalian models of chemically induced primary malignancies exploitable for imaging-based preclinical theragnostic research. *Quant. Imaging Med. Surg.* **2015**, *5* (5), 708−729.
(85) Sirerol, J. A.; Feddi, F.; Mena, S.; Rodriguez, M. L.; Sirera, P.; Aupí, M.; Pérez, S.; Asensi, M.; Ortega, A.; Estrela, J. M. Topical treatment with pterostilbene, a natural phytoalexin, effectively protects hairless mice against UVB radiation-induced skin damage and carcinogenesis. *Free Radical Biol. Med.* **2015**, *85*, 1−11.
(86) Li, H.; Jiang, N.; Liang, B.; Liu, Q.; Zhang, E.; Peng, L.; Deng, H.; Li, R.; Li, Z.; Zhu, H. Pterostilbene protects against UVB-induced photo-damage through a phosphatidylinositol-3-kinase-dependent Nrf2/ARE pathway in human keratinocytes. *Redox Rep.* **2017**, *22* (6), 501−507.
(87) Taguchi, K.; Motohashi, H.; Yamamoto, M. Molecular mechanisms of the Keap1-Nrf2 pathway in stress response and cancer evolution. *Genes Cells* **2011**, *16* (2), 123−140.
(88) Bhakkiyalakshmi, E.; Dineshkumar, K.; Karthik, S.; Sireesh, D.; Hopper, W.; Paulmurugan, R.; Ramkumar, K. M. Pterostilbene-mediated Nrf2 activation: Mechanistic insights on Keap1:Nrf2 interface. *Bioorg. Med. Chem.* **2016**, *24* (16), 3378−3386.
(89) Harun, Z.; Ghazali, A. R. Potential chemoprevention activity of pterostilbene by enhancing the detoxifying enzymes in the HT-29 cell line. *Asian Pac. J. Cancer Prev.* **2012**, *13* (12), 6403−6407.
(90) Shimada, T.; Hayes, C. L.; Yamazaki, H.; Amin, S.; Hecht, S. S.; Guengerich, F. P.; Sutter, T. R. Activation of chemically diverse procarcinogens by human cytochrome P-450 1B1. *Cancer Res.* **1996**, *56* (13), 2979−2984.
(91) Mikstacka, R.; Rimando, A. M.; Szalaty, K.; Stasik, K.; Baer-Dubowska, W. Effect of natural analogues of trans-resveratrol on cytochromes P4501A2 and 2E1 catalytic activities. *Xenobiotica* **2006**, *36* (4), 269−285.
(92) Mikstacka, R.; Przybylska, D.; Rimando, A. M.; Baer-Dubowska, W. Inhibition of human recombinant cytochromes P450 CYP1A1 and CYP1B1 by trans-resveratrol methyl ethers. *Mol. Nutr. Food Res.* **2007**, *51* (5), 517−524.
(93) Albassam, A. A.; Frye, R. F. Effect of pterostilbene on in vitro drug metabolizing enzyme activity. *Saudi Pharm. J.* **2019**, *27* (3), 406−412.
(94) Danial, N. N.; Korsmeyer, S. J. Cell death: critical control points. *Cell* **2004**, *116*, 205−219.
(95) Klein, G. Cancer, apoptosis, and nonimmune surveillance. *Cell Death Differ.* **2004**, *11* (1), 13−17.
(96) Ghosh, A. P.; Klocke, B. J.; Ballestas, M. E.; Roth, K. A. CHOP potentially co-operates with FOXO3a in neuronal cells to regulate PUMA and BIM expression in response to ER stress. *PLoS One* **2012**, *7* (6), No. e39586.
(97) Chakraborty, A.; Gupta, N.; Ghosh, K.; Roy, P. In vitro evaluation of the cytotoxic, anti-proliferative and anti-oxidant properties of pterostilbene isolated from Pterocarpus marsupium. *Toxicol. In Vitro* **2010**, *24* (4), 1215−1228.

https://dx.doi.org/10.1021/acs.jafc.9b07860
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

(98) Priego, S.; Feddi, F.; Ferrer, P.; Mena, S.; Benlloch, M.; Ortega, A.; Carretero, J.; Obrador, E.; Asensi, M.; Estrela, J. M. Natural polyphenols facilitate elimination of HT-29 colorectal cancer xenografts by chemoradiotherapy: a Bcl-2- and superoxide dismutase 2-dependent mechanism. *Mol. Cancer Ther.* **2008**, *7* (10), 3330−3342.
(99) McCormack, D. E.; Mannal, P.; McDonald, D.; Tighe, S.; Hanson, J.; McFadden, D. Genomic analysis of pterostilbene predicts its antiproliferative effects against pancreatic cancer in vitro and in vivo. *J. Gastrointest. Surg.* **2012**, *16* (6), 1136−1143.
(100) Hung, C.-M.; Liu, L.-C.; Ho, C.-T.; Lin, Y.-C.; Way, T.-D. Pterostilbene enhances trail-induced apoptosis through the induction of death receptors and downregulation of cell survival proteins in TRAIL-resistance triple negative breast cancer cells. *J. Agric. Food Chem.* **2017**, *65* (51), 11179−11191.
(101) van Noesel, M. M.; van Bezouw, S.; Salomons, G. S.; Voute, P. A.; Pieters, R.; Baylin, S. B.; Herman, J. G.; Versteeg, R. Tumor-specific down-regulation of the tumor necrosis factor-related apoptosis-inducing ligand decoy receptors DcR1 and DcR2 is associated with dense promoter hypermethylation. *Cancer Res.* **2002**, *62* (7), 2157−2161.
(102) Pan, M. H.; Chang, Y. H.; Badmaev, V.; Nagabhushanam, K.; Ho, C. T. Pterostilbene induces apoptosis and cell cycle arrest in human gastric carcinoma cells. *J. Agric. Food Chem.* **2007**, *55* (19), 7777−7785.
(103) Feng, Y.; Yang, Y.; Fan, C.; Di, S.; Hu, W.; Jiang, S.; Li, T.; Ma, Z.; Chao, D.; Feng, X.; Xin, Z.; Pang, S.; Li, X.; Yan, X. Pterostilbene inhibits the growth of human esophageal cancer cells by regulating endoplasmic reticulum stress. *Cell. Physiol. Biochem.* **2016**, *38* (3), 1226−1244.
(104) Ma, Z.; Yang, Y.; Di, S.; Feng, X.; Liu, D.; Jiang, S.; Hu, W.; Qin, Z.; Li, Y.; Lv, J.; Fan, C.; Yan, X.; Li, X. Pterostilbene exerts anticancer activity on non-small-cell lung cancer via activating endoplasmic reticulum stress. *Sci. Rep.* **2017**, *7* (1), 8091.
(105) Lin, L.; Baehrecke, E. H. Autophagy, cell death, and cancer. *Mol. Cell. Oncol.* **2015**, *2* (3), No. e985913.
(106) Chen, R. J.; Lee, Y. H.; Yeh, Y. L.; Wu, W. S.; Ho, C. T.; Li, C. Y.; Wang, B. J.; Wang, Y. J. Autophagy-inducing effect of pterostilbene: A prospective therapeutic/preventive option for skin diseases. *J. Food Drug Anal.* **2017**, *25* (1), 125−133.
(107) Wang, Y.; Ding, L.; Wang, X.; Zhang, J.; Han, W.; Feng, L.; Sun, J.; Jin, H.; Wang, X. J. Pterostilbene simultaneously induces apoptosis, cell cycle arrest and cyto-protective autophagy in breast cancer cells. *Am. J. Transl. Res.* **2012**, *4* (1), 44−51.
(108) He, J. L.; Dong, X. H.; Li, Z. H.; Wang, X. Y.; Fu, Z. A.; Shen, N. 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.* **2018**, *17* (3), 4406−4414.
(109) Ko, C. P.; Lin, C. W.; Chen, M. K.; Yang, S. F.; Chiou, H. L.; Hsieh, M. J. Pterostilbene induce autophagy on human oral cancer cells through modulation of Akt and mitogen-activated protein kinase pathway. *Oral Oncol.* **2015**, *51* (6), 593−601.
(110) Yu, C. L.; Yang, S. F.; Hung, T. W.; Lin, C. L.; Hsieh, Y. H.; Chiou, H. L. 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.* **2019**, *10* (6), 418.
(111) Sherr, C. J.; Bartek, J. Cell cycle − Targeted cancer therapies. *Annu. Rev. Cancer Biol.* **2017**, *1* (1), 41−57.
(112) Dhar, S.; Kumar, A.; Rimando, A. M.; Zhang, X.; Levenson, A. S. Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer. *Oncotarget* **2015**, *6* (29), 27214−27226.
(113) Brandmaier, A.; Hou, S. Q.; Shen, W. H. Cell cycle control by PTEN. *J. Mol. Biol.* **2017**, *429* (15), 2265−2277.
(114) Yu, D.; Zhang, Y.; Chen, G.; Xie, Y.; Xu, Z.; Chang, S.; Hu, L.; Li, B.; Bu, W.; Wang, Y.; Xiao, W.; Sun, X.; Chang, G.; Gao, L.; Qiang, S.; Wu, X.; Zhu, W.; Shi, J. Targeting the PI3K/Akt/mTOR signaling pathway by pterostilbene attenuates mantle cell lymphoma progression. *Acta Biochim. Biophys. Sin. (Shanghai).* **2018**, *50* (8), 782−792.
(115) Tan, K. T.; Chen, P. W.; Li, S.; Ke, T. M.; Lin, S. H.; Yang, C. C. Pterostilbene inhibits lung squamous cell carcinoma growth in vitro and in vivo by inducing S phase arrest and apoptosis. *Oncol. Lett.* **2019**, *18* (2), 1631−1640.
(116) Lee, H.; Kim, Y.; Jeong, J. H.; Ryu, J.-H.; Kim, W.-Y. ATM/CHK/p53 Pathway Dependent Chemopreventive and therapeutic activity on lung cancer by pterostilbene. *PLoS One* **2016**, *11* (9), No. e0162335.
(117) Kong, Y.; Chen, G.; Xu, Z.; Yang, G.; Li, B.; Wu, X.; Xiao, W.; Xie, B.; Hu, L.; Sun, X.; Chang, G.; Gao, M.; Gao, L.; Dai, B.; Tao, Y.; Zhu, W.; Shi, J. Pterostilbene induces apoptosis and cell cycle arrest in diffuse large B-cell lymphoma cells. *Sci. Rep.* **2016**, *6*, 37417.
(118) Gupta, G. P.; Massague, J. Cancer metastasis: building a framework. *Cell* **2006**, *127* (4), 679−695.
(119) Schneider, J. G.; Alosi, J. A.; McDonald, D. E.; McFadden, D. W. Effects of pterostilbene on melanoma alone and in synergy with inositol hexaphosphate. *Am. J. Surg.* **2009**, *198* (5), 679−684.
(120) Butt, N. A.; Kumar, A.; Dhar, S.; Rimando, A. M.; Akhtar, I.; Hancock, J. C.; Lage, J. M.; Pound, C. R.; Lewin, J. R.; Gomez, C. R.; Levenson, A. S. Targeting MTA1/HIF-1alpha signaling by pterostilbene in combination with histone deacetylase inhibitor attenuates prostate cancer progression. *Cancer Med.* **2017**, *6* (11), 2673−2685.
(121) Dhar, S.; Kumar, A.; Zhang, L.; Rimando, A. M.; Lage, J. M.; Lewin, J. R.; Atfi, A.; Zhang, X.; Levenson, A. S. Dietary pterostilbene is a novel MTA1-targeted chemopreventive and therapeutic agent in prostate cancer. *Oncotarget* **2016**, *7* (14), 18469−18484.
(122) Li, K.; Dias, S. J.; Rimando, A. M.; Dhar, S.; Mizuno, C. S.; Penman, A. D.; Lewin, J. R.; Levenson, A. S. Pterostilbene acts through metastasis-associated protein 1 to inhibit tumor growth, progression and metastasis in prostate cancer. *PLoS One* **2013**, *8* (3), No. e57542.
(123) Xing, F.; Liu, Y.; Sharma, S.; Wu, K.; Chan, M. D.; Lo, H.-W.; Carpenter, R. L.; Metheny-Barlow, L. J.; Zhou, X.; Qasem, S. A.; Pasche, B.; Watabe, K. Activation of the c-met pathway mobilizes an inflammatory network in the brain microenvironment to promote brain metastasis of breast cancer. *Cancer Res.* **2016**, *76* (17), 4970−4980.
(124) Hong, B. H.; Wu, C. H.; Yeh, C. T.; Yen, G. C. Invadopodia-associated proteins blockade as a novel mechanism for 6-shogaol and pterostilbene to reduce breast cancer cell motility and invasion. *Mol. Nutr. Food Res.* **2013**, *57* (5), 886−895.
(125) Pan, M. H.; Chiou, Y. S.; Chen, W. J.; Wang, J. M.; Badmaev, V.; Ho, C. T. Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. *Carcinogenesis* **2009**, *30* (7), 1234−1242.
(126) Lin, C. W.; Chou, Y. E.; Chiou, H. L.; Chen, M. K.; Yang, W. E.; Hsieh, M. J.; Yang, S. F. Pterostilbene suppresses oral cancer cell invasion by inhibiting MMP-2 expression. *Expert Opin. Ther. Targets* **2014**, *18* (10), 1109−1120.
(127) Kalluri, R.; Weinberg, R. A. The basics of epithelial-mesenchymal transition. *J. Clin. Invest.* **2009**, *119* (6), 1420−1428.
(128) Su, C.-M.; Lee, W.-H.; Wu, A. T.H.; Lin, Y.-K.; Wang, L.-S.; Wu, C.-H.; Yeh, C.-T. Pterostilbene inhibits triple-negative breast cancer metastasis via inducing microRNA-205 expression and negatively modulates epithelial-to-mesenchymal transition. *J. Nutr. Biochem.* **2015**, *26* (6), 675−685.
(129) Mak, K. K.; Wu, A. T. H.; Lee, W. H.; Chang, T. C.; Chiou, J. F.; Wang, L. S.; Wu, C. H.; Huang, C. Y. F.; Shieh, Y. S.; Chao, T. Y.; Ho, C. T.; Yen, G. C.; Yeh, C. T. Pterostilbene, a bioactive component of blueberries, suppresses the generation of breast cancer stem cells within tumor microenvironment and metastasis via modulating NF-kappaB/microRNA 448 circuit. *Mol. Nutr. Food Res.* **2013**, *57* (7), 1123−1134.
(130) Huang, Y.; Du, J.; Mi, Y.; Li, T.; Gong, Y.; Ouyang, H.; Hou, Y. Long non-coding RNAs contribute to the inhibition of proliferation

https://dx.doi.org/10.1021/acs.jafc.9b07860
J. Agric. Food Chem. XXXX, XXX, XXX−XXX

and EMT by pterostilbene in human breast cancer. *Front. Oncol.* **2018**, *8*, 629.
(131) Ferrer, P.; Asensi, M.; Segarra, R.; Ortega, A.; Benlloch, M.; Obrador, E.; Varea, M. T.; Asensio, G.; Jorda, L.; Estrela, J. M. Association between pterostilbene and quercetin inhibits metastatic activity of B16 melanoma. *Neoplasia* **2005**, *7* (1), 37−47.
(132) Tolba, M. F.; Abdel-Rahman, S. Z. Pterostilbine, an active component of blueberries, sensitizes colon cancer cells to 5-fluorouracil cytotoxicity. *Sci. Rep.* **2015**, *5*, 15239.
(133) Mannal, P.; McDonald, D.; McFadden, D. Pterostilbene and tamoxifen show an additive effect against breast cancer in vitro. *Am. J. Surg.* **2010**, *200* (5), 577−580.
(134) Kostin, S. F.; McDonald, D. E.; McFadden, D. W. Inhibitory effects of (−)-epigallocatechin-3-gallate and pterostilbene on pancreatic cancer growth in vitro. *J. Surg. Res.* **2012**, *177* (2), 255−262.
(135) Wu, C. H.; Hong, B. H.; Ho, C. T.; Yen, G. C. Targeting cancer stem cells in breast cancer: potential anticancer properties of 6-shogaol and pterostilbene. *J. Agric. Food Chem.* **2015**, *63* (9), 2432−2441.
(136) Singh, P.; Arora, D.; Shukla, Y. Enhanced chemoprevention by the combined treatment of pterostilbene and lupeol in B[a]P-induced mouse skin tumorigenesis. *Food Chem. Toxicol.* **2017**, *99*, 182−189.
(137) Huang, X. Y.; Zhang, S. Z.; Wang, W. X. Enhanced antitumor efficacy with combined administration of astragalus and pterostilbene for melanoma. *Asian Pac. J. Cancer Prev.* **2014**, *15* (3), 1163−1169.
(138) Huang, C. S.; Ho, C. T.; Tu, S. H.; Pan, M. H.; Chuang, C. H.; Chang, H. W.; Chang, C. H.; Wu, C. H.; Ho, Y. S. Long-term ethanol exposure-induced hepatocellular carcinoma cell migration and invasion through lysyl oxidase activation are attenuated by combined treatment with pterostilbene and curcumin analogues. *J. Agric. Food Chem.* **2013**, *61* (18), 4326−4335.
(139) Paul, S.; DeCastro, A. J.; Lee, H. J.; Smolarek, A. K.; So, J. Y.; Simi, B.; Wang, C. X.; Zhou, R.; Rimando, A. M.; Suh, N. Dietary intake of pterostilbene, a constituent of blueberries, inhibits the beta-catenin/p65 downstream signaling pathway and colon carcinogenesis in rats. *Carcinogenesis* **2010**, *31* (7), 1272−1278.

https://dx.doi.org/10.1021/acs.jafc.9b07860
J. Agric. Food Chem. XXXX, XXX, XXX−XXX