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Anti−inflammatory and anti−cancer potential of pterostilbene: A review

Omchit Surien[1], Siti Fathiah Masre[1], Dayang Fredalina Basri[2], Ahmad Rohi Ghazali[1]✉

[1]*Centre for Toxicology and Health Risk Studies (CORE), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300, Kuala Lumpur, Malaysia*

[2]*Centre of Diagnostic, Therapeutic & Investigative Studies (CODTIS), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300, Kuala Lumpur, Malaysia*

ABSTRACT

Pterostilbene is a natural compound that can be found in various food plants such as blueberries, grapes, and peanuts. It has also been reported to be extracted from *Pterocarpus indicus*, a tree species native to India and Southeast Asia. Pterostilbene exhibits various pharmacological activities such as antioxidants, anti-proliferation, anti-microbial, and anti-inflammatory activities with favorable pharmacokinetic properties, such as high oral bioavailability and longer half-life. The anti-inflammatory effect of pterostilbene has been reported to contribute to its therapeutic effects in many chronic inflammatory diseases. Besides, pterostilbene has anti-cancer activity on various types of cancers due to its ability to induce cell cycle arrest and apoptosis. Hence, in this review, we discuss the anti-inflammatory and anti-cancer activities of pterostilbene in preclinical studies.

KEYWORDS: Pterostilbene; Anti-cancer; NF-κB; Anti-inflammation; Natural product; *Pterocarpus indicus*

1. Introduction

Polyphenols are naturally occurring compounds that can be found widely in plants and are further divided into a few polyphenol subtypes, including stilbenes, lignans, flavonoids, hydroxybenzoic acids, and hydroxycinnamic acids[1]. Resveratrol and pterostilbene are the two crucial polyphenol stilbenes that have attracted the interest of medical researchers in recent years[2]. One of the important medicinal benefits is to reduce the risk of or slow down the development of various diseases, as pterostilbene has been proven to exhibit protective effects against cardiovascular disease, cancer, and neurodegenerative disease[3−5].

2. Pterostilbene

Pterostilbene was first isolated from the deciduous tree of *Pterocarpus marsupium* in 1940, which is native to India[6]. Other than *Pterocarpus marsupium*, pterostilbene also can be found in other *Pterocarpus* tree species such as *Pterocarpus indicus* (narra), which is native to Southeast Asia, including Malaysia, Indonesia, and Thailand[7,8]. Pterostilbene or its chemical name *trans*-3,5-dimethoxy-4′-hydroxystilbene with the molecular structure of $C_{16}H_{16}O_3$ of 256.3 g/mol molecular weight is a dimethyl ether analog of the well-studied compound of resveratrol[9,10]. Resveratrol and pterostilbene were classified under the same family polyphenolic secondary metabolite of stilbenes. This is because these two compounds share the common chemical structure properties of the stilbene family, where both compounds consist of a 14-carbon skeleton with two benzene rings, and these two benzene rings are connected through an ethylene bridge[11]. Resveratrol and pterostilbene have been proven to exhibit various pharmacological properties that benefit human health, such as anti-inflammation and antioxidants[12,13]. Interestingly, pterostilbene has better pharmacokinetic properties regarding half-life as it has a longer half-life of 105 min, but resveratrol has only a 14 min half-life[14,15]. In addition, pterostilbene has a better bioavailability than other stilbene

✉To whom correspondence may be addressed. E-mail: rohi@ukm.edu.my

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compounds such as resveratrol[16].

The differences in the pharmacokinetics of resveratrol and pterostilbene are due to the distinction in their chemical structures as resveratrol consists of three hydroxyl groups (-OH), but pterostilbene has one hydroxyl group and two methoxy groups (-OCH_3) as shown in Figure 1[2]. The existence of the two methoxy groups on the chemical structure of pterostilbene increases the compound's lipophilicity, thus enhancing the oral absorption of pharmacokinetics (oral bioavailability). This makes pterostilbene more favorable for cellular uptake, protects it from degradation, and increases its stability[14,17]. The toxicological profile of pterostilbene documented that it is safe even at a high dose of up to 3 000 mg/kg in mice for 28 d[18]. In addition, a clinical study on the toxic effect of pterostilbene consumption in 80 healthy volunteers proved that consuming pterostilbene up to 250 mg/kg for 6-8 weeks was safe. The study findings based on biochemical analysis showed that pterostilbene did not cause any adverse reactions and no abnormalities in the liver or kidneys[19]. Moreover, the anti-inflammatory effect of pterostilbene is one of its medicinal benefits that should be explored to prevent or treat various inflammation-related diseases[20,21]. Our review will focus on the anti-inflammatory and anti-cancer properties of pterostilbene.

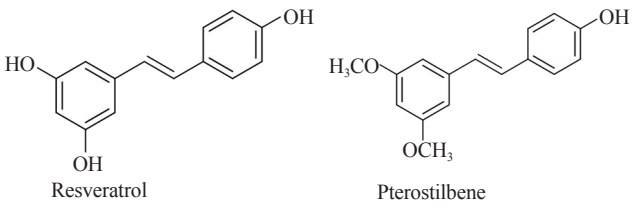

Figure 1. The chemical structures of pterostilbene and resveratrol (created with ChemDraw Professional 15.0.).

3. Inflammation

Inflammation is an ancient biological process that is required to maintain homeostasis by protecting the host from pathogens and tissue injury and involving tissue repair, regeneration, and remodeling[22].

3.1. Acute inflammation

Acute inflammation is the inflammation response that is responsible for protecting our body from harmful conditions, including exposure to pathogens or injury. It is a self-limiting response in which once the infection or injury has been successfully controlled or eliminated, the inflammation response resolves, followed by restoring affected tissue to its normal structural and functional state[23]. In the physiological state, there are several mechanisms to control the inflammation by the immune system, such as inhibition of the pro-inflammatory signaling, and failure to manage or resolve inflammation response results in the pathological condition of chronic inflammation[24]. The failure of acute inflammation to resolve during the physiological process can lead to the uncontrollable and persistent inflammatory response known as chronic inflammation, which is responsible for various pathological processes or disease development[25,26].

3.2. Chronic inflammation

Chronic inflammation is a pathological condition where the active inflammation process persists for an extended period, resulting in fibrosis, tissue destruction, and the arrival of mononuclear inflammatory cells such as macrophages, lymphocytes, and plasma cells to the site of inflammation[27]. Cancer is one of the diseases that have a strong association with unresolved or chronic inflammation[28]. The link between inflammation and carcinogenesis can be seen clearly as inflammatory cells and mediators are crucial components of tumor microenvironments. The tumor microenvironment consists of the cellular and noncellular components surrounding and nourishing the tumor cells, including adipose cells, immune cells, blood, and lymphatic vessels[29]. Many types of immune cells comprise the non-malignant components of tumor environments, including T cells, mast cells, macrophages, natural killer cells, dendritic cells, and others[30]. Among all these immune cells, the macrophage is dominant, present abundantly, and is involved in all stages of tumor development known as tumor-associated macrophages. Most inflammatory mediators in the tumor microenvironment, including growth factors, cytokines, and chemokines, are produced mainly by tumor-associated macrophages[31]. Hence this further supported the fact that uncontrolled or chronic inflammation can lead to pathological processes such as malignant growth and tumor initiation, as well as chronic inflammation causes the continuous production of growth factors and oxidative stress, which cause damage to the deoxyribonucleic acid (DNA) of proliferating cells that will result in irreversible genomic changes[32,33]. In addition to tumor initiation, inflammation also is known to be involved in other stages of carcinogenesis, such as tumor promotion, malignant transformation, and metastasis as inflammatory mediators such as chemokines, prostaglandins, proteolytic enzymes, cytokines, and free radicals can stimulate cancer development[34].

Carcinogenesis and inflammation conditions share common developmental pathways characterized by increased cell proliferation, migration, survival, and angiogenesis[35,36]. The risk of colorectal cancer is ten times higher in people who have inflammation diseases, including chronic ulcerative colitis and Crohn's disease[37]. Therefore, a better understanding of the biological pathways that link inflammation with carcinogenesis is crucial for developing specific and effective targeted therapies

or preventing cancer that focuses on inflammation. For this reason, the molecular mechanisms of inflammation linked to carcinogenesis have gained increasing attention from researchers in cancer studies[38]. One of the most widely studied inflammatory pathways in cancer studies is the NF-κB inflammatory pathway, as the abnormalities in this pathway have been reported in numerous types of human cancer, such as lung, pancreatic, skin, and liver cancer[39–42]. The NF-κB is a protein complex that is involved in many important events like innate and adaptive immune responses to promote cell proliferation, angiogenesis, metastasis, and the suppression of cell death *via* apoptosis[43].

4. NF–κB inflammatory signaling pathway

The NF-κB is a significant transcription factor that can regulate the expression of various essential genes in biological processes. Transcription factors are a family of proteins that can bind to specific targeted DNA sequences and control the translation process of that DNA into the messenger RNA (mRNA)[44]. The NF-κB plays a major role in the regulation of genes that are responsible for inflammatory responses such as inducible nitric oxide synthetase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α) and many interleukins (IL-1, IL-2, IL-6, IL-8, IL-12)[45,46]. It is also a Rel family transcription factor and mammalian cells express five types of NF-κB protein subunits, namely p65 (RelA), RelB, c-Rel, NF-κB1 (p105/50), and NF-κB2 (p100/52)[47,48]. The activation process of NF-κB can be divided into two main signaling pathways: the canonical, also known as classical, and non-canonical (or alternative) pathways[49,50]. The canonical pathway involves the activation of three subunits of NF-κB, including NF-κB1 p50, RelA, and cRel, hence, these three subunits of NF-κB are also known as canonical NF-κB family members[51]. In contrast to the canonical pathway, the non-canonical NF-κB pathway targets the activation of p52/RelB NF-κB with the involvement of NF-κB2 p100 processing[52].

5. Anti–cancer effects of pterostilbene

Numerous studies have investigated the anti-cancer and chemopreventive effects of pterostilbene on various types of cancer *via* its anti-inflammation and other pharmacological properties. An *in vitro* study reported that pterostilbene exerts anti-cancer effects on human oral squamous cell carcinoma SCC-9 by inhibiting cell migration and invasion. Its further investigation showed that pterostilbene reduced the phosphorylation of IκBα, thus suppressing the ability of NF-κB to bind to its targeted genes of DNA or DNA binding activity. Pterostilbene also inhibited the upstream regulators of the NF-κB pathway of MAPKs family including ERK, JNK, and p38 in the SCC-9 cell line[53].

The *in vivo* investigation of the azoxymethane-induced colon cancer rat model revealed that the dietary intake of pterostilbene could downregulate the NF-κB pathway. In addition to that, pterostilbene also reduced the production and expression of pro-inflammatory cytokines and enzymes of the NF-κB-related signaling pathway, including TNF-α, IL-1β, iNOS, IL-4, and COX-2 in rats. Other than the anti-inflammatory action, pterostilbene also exerts chemopreventive effects by suppressing the development of colon cancer and reducing the incidence and multiplicity of tumors compared to the control group. Cell proliferation was inhibited by the downregulation of proliferating cell nuclear antigen and cyclin D1 protein expression[54]. Another recent study showed that pterostilbene exhibited antitumor activity in both *in vitro* and *in vivo* models. The *in vitro* results showed that pterostilbene caused cell cycle arrest at the G_2/M phase and induced apoptosis by upregulating the protein expression of apoptosis-related protein p53 in human colorectal cancer cell line CL187. Moreover, the *in vivo* results revealed that pterostilbene reduced tumor volume and tumor weight and increased tumor inhibition rate in a dose-dependent manner in a CL187 xenograft nude mouse model. This study concluded that pterostilbene inhibits the cell proliferation of CL187 by the downregulation of gene and protein expression and activity of Tyrosyl-DNA phosphodiesterase 1 and topoisomerase 1 enzymes[55].

Other than the modulation of the inflammation pathway, pterostilbene has been proven to exert anti-cancer or chemopreventive effects *via* regulation of other pathways including the cell cycle and cell death. Pterostilbene caused cytotoxic effects on the human lung squamous cell carcinoma cell line (H520) by inducing cell cycle arrest and cell death through apoptosis. Pterostilbene downregulated the protein expression of cell cycle regulators such as cyclin A and E which are essential for cell cycle progression, and upregulated cell cycle inhibitors of p21 and p27 to induce cell cycle arrest. Moreover, the protein expression of pro-apoptotic proteins such as Bax and cytochrome-c was upregulated, while the anti-apoptotic protein Bcl-2 was downregulated in pterostilbene-treated cells. These results indicate that pterostilbene suppresses H520 cell growth by inducing apoptosis and cell cycle arrest. Intraperitoneal injection of pterostilbene at 50 mg/kg also significantly reduced tumor volume and weight in a xenograft mouse model of H520 cells[56]. Pterostilbene promoted cell cycle arrest to disrupt and delay the development of lung squamous cell carcinoma in an *N*-nitroso-*tris*-chloroethylurea-induced lung cancer mouse model. In addition, it downregulated the protein expression of cyclin E2 and D1 and upregulated the protein expression of cell cycle inhibitors including p53, p21, and p27[57]. Moreover, the histopathological findings also revealed that pterostilbene could inhibit the development of lung squamous cell carcinoma. The pterostilbene treated mice mostly

developed pre-malignant lesions of lung squamous cell carcinoma including hyperplasia and dysplasia compared to the cancer control group that displayed histological features of squamous cell carcinoma such as formation of keratin pearls and increased nucleas:cytoplasm ratio[58].

Pterostilbene suppressed the growth and colony formation of a few cervical cancer cell lines including the HeLa, CaSki, and SiHa. Further study on molecular mechanisms of the inhibitory action of pterostilbene against the HeLa cell line revealed that pterostilbene promoted cell cycle arrest and apoptosis. Pterostilbene induced cell cycle arrest on HeLa cells by the downregulation of the expression of cyclin B1 and E1 and upregulation of p53 and p21 expression. Pterostilbene induced cell apoptosis by the upregulation of apoptosis caspases including activated caspase-9 and-3 in HeLa cells. In contrast, the anti-apoptotic proteins of Bcl-2 and Bcl-XL were downregulated in HeLa cells treated with pterostilbene. Moreover, pterostilbene reduced the invasiveness of HeLa cells, as evidenced by the reduced percentage of migrated and invaded cells. The protein expression of metalloproteinases-2 and -9 that participate in tumor invasion and metastasis was also downregulated by pterostilbene[16].

The anti-cancer effects of pterostilbene have also been reported in gallbladder cancer. Pterostilbene inhibited cell proliferation and induced apoptosis of various gallbladder cell lines including GBC-SD, SGC-996, and NOZ cells. The *in vivo* results indicated that pterostilbene inhibited tumor growth by reducing the tumor weight of GBC-SD cells in the xenograft mouse model. The molecular investigations on both *in vitro* and *in vivo* models revealed that pterostilbene reduced the migration and invasiveness of gallbladder cancer through the downregulation of the expression of epithelial-mesenchymal transition-related proteins including vimentin, β-catenin, and N-adherin and upregulation of zonula occludens protein-1 expression. Pterostilbene also inhibited the activation of PI3K/Akt *via* the downregulation of phosphorylated PI3K/Akt protein expression[59]. Pterostilbene reduced the average number and volume of tumors per mouse in 7,12-dimethylbenz(a)anthracene/12-*O*-tetradecanoylphorbol-13-acetate (DMBA/TPA) induced skin squamous cell carcinoma mouse model. The histopathological observations revealed that pterostilbene prevented invasion of the basement membrane of the epidermis layer of skin and decreased nuclear pleomorphism, and reduced the thickness of the epidermis layer compared to cancer control mice without pterostilbene treatment. The protein expression of Ki-67 as a cell proliferation marker was reduced in tumors of mice treated with pterostilbene[60].

Pterostilbene also exhibited anti-cancer effects against human cholangiocarcinoma cell line (HCCC-9810) by reducing cell viability and colony formation. Further investigations revealed that pterostilbene could induce cell cycle arrest at the S phase and apoptosis, and upregulated the expression of cyclin A2 and E1. It also induced autophagy in HCCC-9810 cells by the upregulation of the expression of autophagy-related 5 and Beclin-1. However, due to the dual roles of autophagy as a tumor suppressor or promoter, further investigation is needed to prove that autophagy-inducing effects of pterostilbene can lead to inhibition of cell proliferation, not promotion of cancer cell survival. The *in vivo* xenograft mouse model results showed that pterostilbene could suppress the growth of HCCC-9810 cells by reducing tumor weight, size, and volume[61]. Wawszczyk *et al*. reported that pterostilbene reduced the proliferation of both amelanotic (C32) and melanotic (A2508) melanoma cancer cells in a dose-dependent manner. The cycle arrest at the S phase was induced in pterostilbene-treated C32 and A2508 cells, as confirmed by the downregulation of gene expression of cyclin D1 and the upregulation of gene expression of p21. Pterostilbene also promoted apoptosis in C32 cell line by upregulating the pro-apoptotic gene expression of Bax and increasing caspase-3 activity[62]. Table 1 summarizes the anti-cancer effects of pterostilbene *via* various molecular mechanisms including anti-inflammation, cell cycle arrest, and apoptosis.

6. Anti–inflammation of pterostilbene in diseases and injuries

Many studies have explored the anti-inflammation of pterostilbene and the role of the NF-κB signaling pathway in various inflammation-related pathological conditions and diseases. A recent study showed that pterostilbene could suppress NF-κB activation by inhibiting the degradation process of IκBα in a mouse model with TPA-induced skin inflammation. Pterostilbene also downregulated the expression of NF-κB downstream effectors of COX and iNOS and upstream regulators of MAPKs including ERK, JNK, and p38 to inhibit the skin inflammation response[63]. Pterostilbene suppresses osteoclastogenesis by suppressing the differentiation of monocytes to become osteoclasts. Further molecular investigation revealed that pterostilbene prevents the NF-κB translocation into the nucleus by blocking the phosphorylation of IκBα and downregulates the expression of ERK and JNK in RAW264.7 cells[64].

Furthermore, pterostilbene showed protective and anti-inflammatory effects against the oxidative stress induced injury in the artery of the atherosclerosis rat model by reducing the serum level of pro-inflammatory mediators IL-1, TNF-α, and IL-6. The *in vitro* assay on endothelial cells also showed similar results as evidenced by increased cell viability and significantly lowered levels of IL-1, TNF-α, and IL-6 following pterostilbene treatment[65]. Many previous studies have reported the protective effects of pterostilbene against various pathological conditions related to inflammation through its anti-inflammatory effects. A previous study demonstrated that pterostilbene reduces the infarcted area, brain edema, and neuronal cell loss of the brain in neonatal rats,

Table 1. Anti-cancer effects of pterostilbene on various types of cancer.

Cancer type	Type of study	Route of administration, dose, and duration	Results	Ref
Oral squamous cell carcinoma	SCC-9 cell line	(5, 10, 20, 40, and 80 μM) for 24, 48 and 72 h	↓ cell proliferation, phosphorylation IκBα; NF-κB activation; binding of NF-κB to the DNA ↓ NF-κB of MAPKs family including ERK, JNK, and p38	[53]
Colon cancer	Azoxymethan-induced colon cancer rat model	40 p.p.m. (0.004%) of pterostilbene in the diet	↓ cell proliferation, NF-κB, iNOS, TNF-α, IL-1β, IL-4 and COX-2	[54]
Colon cancer	Human colorectal cancer cell line CL187 CL187 xenograft mouse model	1, 10, 20, 30, 50, and 100 μM for 48 h Intraperitoneal injection of 25, 50, 100, and 200 mg/kg once a day for 31 days	↓ cell viability ↑ cell cycle arrest and apoptosis ↓ tumor volume and tumor weight ↑ tumor inhibition rate	[55]
Lung squamous cell carcinoma	Human lung squamous cell carcinoma H520 cell line Xenograft mouse model	12.5, 25, and 50 μM for 24 and 48 h Intraperitoneal injection (50 mg/kg) for 38 days	↑ cell cycle inhibitors of p21 and p27 and pro-apoptotic Bax and cytochrome-c ↓ cell cycle regulator cyclin A and E, and anti-apoptotic Bcl-2 ↓ tumor weight and volume	[56]
Lung squamous cell carcinoma	NTCU-induced lung squamous cell carcinoma mouse model	Intraperitoneal injection of 10 and 50 mg/kg of pterostilbene for 26 weeks (twice a week)	↓ cell cycle regulator cyclin D1 and E2 ↑ cell cycle inhibitors of p53, p21, and p27 Histopathological findings demonstrated that pterostilbene delayed the development of lung cancer	[57,58]
Cervical cancer	HeLa, CaSki, and SiHa	6.25, 12.5, 25, 50, 100, and 200 μM for 72 h	↓ cell growth and colony formation HeLa cells: ↑ cleaved or activated caspase-9, -3 and cell cycle inhibitors of p53 and p21 ↓ cell cycle proteins of cyclin B1 and E1 and invasion of MMP-2 and -9	[16]
Gallbladder cancer	GBC-SD, SGC-996 and NOZ cells GBC-SD cell xenograft mouse model	20, 40, and 60 μM for 48 h Intraperitoneal injection of 30 mg/kg pterostilbene once every 2 days for 3 weeks	↓ cell viability and proliferation ↑ apoptosis ↓ EMT (vimentin, β-catenin, N-cadherin), PI3K/Akt signaling pathway ↓ tumor weight ↓ EMT (vimentin, β-catenin, N-cadherin), PI3K/Akt signaling pathway	[59]
Cutaneous squamous cell carcinoma	A chemically DMBA/TPA-induced skin carcinogenesis mouse model	Oral gavage (50 mg/kg twice a week for 24 weeks)	↓ histopathological changes, the volume, and the average number of tumors per mouse ↓ cell proliferation marker of Ki-67	[60]
Biliary tract cancer (cholangiocarcinoma)	Human cholangiocarcinoma cells, HCCC-9810 cell line Xenograft mouse model of HCC-9810 cell line	30, 60, and 120 μM of pterostilbene Intraperitoneal injection of 30 and 60 mg/kg of pterostilbene once every two days for 3 weeks	↓ cell viability and colony formation ↑ cell cycle arrest, apoptosis, and autophagy ↓ tumor weight, size, and volume	[61]
Amelanotic and melanotic skin cancer	Amelanotic (C32) and melanotic human (A2058) cancer cell lines	20, 40, and 60 μM of pterostilbene for 12 h	↓ cell proliferation and gene expression of cyclin D1 ↑ cell cycle arrest on the S phase, gene expression of p21, and caspase-3 activity	[62]

TNF-α: tumor necrosis factor-alpha; NF-κB: nuclear factor-kappa B; IL-1β: interleukin-1β; IL-6: interleukin-6; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; MAPKs: mitogen-activated protein kinases; ERK: extracellular signal-regulated kinase; JNK: c-Jun *N*-terminal kinases; COX-2: cyclooxygenase-2; iNOS: inducible nitric oxide synthase; DMBA: 12-dimethylbenz(a)anthracene; TPA: 12-*O*-tetra-decanoylphorbol-13-acetate; MMP: matrix metalloproteinases; EMT: epithelial-mesenchymal transition; Bax: Bcl-2-associated X protein; NTCU: *N*-nitroso-tri-chloroethylurea.

therefore protecting them from hypoxic-ischemic brain injury. The anti-inflammation of pterostilbene can be attributed to its inhibition of the NF-κB activation process by downregulating the protein expression of phosphorylated (activated) NF-κB and IκBα and TNF-α[66]. Furthermore, pterostilbene showed protective effects against lipopolysaccharide/*D*-galactosamine-induced acute liver injury by reducing the level of alanine transaminase and aspartate aminotransferase in the liver tissues and serum. The histopathological observations showed that pterostilbene reduced hepatic hemorrhage and inflammatory cell infiltration. The gene expression of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 in the liver tissues was also reduced in pterostilbene-treated mice[67].

Moreover, pterostilbene was reported to reverse the effect of lipopolysaccharide-induced pulmonary fibrosis in the mouse model *via* its anti-inflammatory effect. Pterostilbene suppressed the NF-κB activation by reducing the phosphorylation of NF-κB and IκB. Furthermore, pterostilbene reduced the levels of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, and elevated IL-10 level in the lungs[68]. Zhang *et al*. found that pterostilbene exhibits protective

effects against nephropathy injury in streptozotocin-induced diabetic rats by inhibiting the extracellular matrix and mesangial matrix expansion, reducing the levels of malondialdehyde (MDA) and pro-inflammatory mediators, and enhancing antioxidant levels. Further molecular investigation revealed that pterostilbene blocked the phosphorylation of IκBα and downregulated the protein expression of phosphorylated NF-κB[69]. In a study by Sun *et al*., pterostilbene reduced lipid and protein peroxidation and increased the antioxidant levels in a rat model with intestinal ischemia-reperfusion injury. Furthermore, pterostilbene lowered the NF-κB and COX-2 expression as well as downregulated TNF-α and IL-1β levels[70].

Pterostilbene has been reported to mitigate Complete Freund's adjuvant-induced arthritis in rats as pterostilbene exhibited anti-inflammatory activity by reducing macrophage infiltration and IL-6 and TNF-α levels[71]. Pterostilbene inhibited the progression of 2,4-dinitrochlorobenzene-induced atopic dermatitis mouse model.

Table 2. Effects of pterostilbene on the NF-κB inflammatory signaling pathway in inflammation-related pathological conditions and diseases.

Disease or injury	Type of study	Route of administration, dose, and duration	Results	Ref
Skin inflammation	TPA-induced skin inflammation mouse model	1 and 5 μmol of 25-30 g mouse for 2 and 4 h	↓ translocation of NF-κB into the nucleus, IκBα degradation, COX-2 and iNOS, and MAPKs (ERK, JNK, and p38)	[63]
Bone resorption or osteoclastogenesis	RAW264.7 cell	5, 10, and 20 μM for 2 h	↓ NF-κB translocation, MAPKs of ERK and JNK ↑ IκBα	[64]
Atherosclerosis and endothelial cell injury	High cholesterol diet-induced atherosclerosis rat model (2.5% of cholesterol diet for 8 weeks)	Oral gavage of 10 mg/kg per day of pterostilbene for 4 weeks	↓ atherogenesis and aortic plaques and level of pro-inflammatory mediators of IL-1, TNF-α, and IL-6	[65]
	Endothelial cells of BeNa Culture Collection Beijing, China	1.0 mmol/L for 12 h	↓ NF-κB, IL-1, TNF-α, and IL-6, NF-κB phosphorylation	
Ischemic brain injury	Ligation of the common carotid artery and hypoxic environment induced ischemic brain injury in the neonatal rat model	Oral gavage (12.5, 25, and 50 mg/kg) for 6 days	↓ neuronal cell loss, brain infarction, brain edema, NF-κB and gene and protein expression levels of TNF-α, IL-1β, and IL-6	[66]
Acute liver injury	Lipopolysaccharide/*D*-galactosamine-induced acute liver injury mouse model	Intraperitoneal injection (10, 20, and 40 mg/kg) twice at 12-hour time intervals	↓ histopathological damages and AST and ALT ↓ NF-κB, TNF-α, IL-6, IL-1β	[67]
Early pulmonary fibrosis	Lipopolysaccharide-induced pulmonary fibrosis mouse model	Intraperitoneal injection (12.5, 25, and 50 mg/kg) for 3 days	↓ histopathological lung injury score, hemorrhage, edema, and collagen ↓ NF-κB, TNF-α, IL-1β, IL-6 ↑ IκB and IL-10	[68]
Nephropathy injury	High-fat diet and streptozotocin-induced nephropathy injury in diabetic rats	Oral gavage (5, 10, and 25 mg/kg/day) for 8 weeks	↓ histopathological changes and MDA ↓ phoshorylation of NF-κB and IκBα, serum IL-1β, IL-6, and TNF-α ↑ SOD and GSH-Px	[69]
Intestinal ischemia/reperfusion injury	Clamp-induced intestinal ischemia/reperfusion injury rat model	Oral gavage (20 mg/kg for 5 days)	↓ lipid and protein peroxidation, NF-κB, COX-2, TNF-α, and IL-1β ↑ antioxidant activities (SOD, GSH, CAT, GSH-Px, and GST)	[70]
Arthritis	Complete Freund's adjuvant-induced arthritis rat model	Oral gavage (12.5, 25 and 50 mg/kg for 21 days)	↓ histopathological changes: inflammatory cell infiltration, pannus formation, and bone erosion ↓ IL-6 and TNF-α	[71]
Atopic dermatitis	2,4-dinitrochlorobenzene-induced atopic dermatitis mouse model	0.2%, 0.6% and 1.0% (weight/weight) of pterostilbene for 28 days	↓ dermatitis score, ear, and skin thickness ↓ skin oxidative stress markers of MDA and NO and gene expression of NF-κB, IL-4, IL-6 and TNF-α ↑ skin antioxidant level of SOD, CAT, and GSH	[72]
Colitis	High-fat diet and dextran sulfate sodium-induced colitis mouse model	0.005% and 0.025% of pterostilbene in drinking water for 2 weeks	↓ histopathological changes in the colon ↓ pro-inflammatory mediators of COX-2, IL-1β, IL-6, and TNF-α ↑ protective layer of the colon	[73]
Asthma	Asthmatic mouse induced by ovalbumin	Oral gavage of 30 and 50 mg/kg of pterostilbene for 7 days	↓ inflammatory cells infiltration and oxidative stress marker (MDA) ↑ antioxidants (SOD and CAT) ↑ AMPK/Sirt1and Nrf2/HO-1	[74]

NO: nitric oxide; CAT: catalase; GSH: glutathione; SOD: superoxidase dismutase; GST: glutathione S-transferases; GSH-Px: glutathione peroxidase; MDA: malondialdehyde; TPA: 12-*O*-tetra-decanoylphorbol-13-acetate; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

The dermatitis scoring, ear, and skin thickness were reduced by topical pterostilbene. Pterostilbene also exerted anti-inflammatory effect against atopic dermatitis *via* the reduction in gene expression of NF-κB and its downstream pro-inflammatory mediators such as IL-4, IL-6, and TNF-α. Moreover, pterostilbene reduced MDA and nitric oxide and increased the level of skin antioxidants including catalase (CAT), SOD, and glutathione[72].

The anti-inflammatory effect of pterostilbene has also been shown to protect the colon from the high-fat diet and dextran sulfate sodium-induced colitis mouse model by reducing the formation of crypt foci (ACF) and aberrant crypt, colon necrosis, and fibroblast cell infiltration. Pterostilbene decreased the levels of IL-6, COX-2, IL-1β and TNF-α[73]. Xu *et al*. revealed that pterostilbene ameliorated airway inflammation and hyperresponsiveness in the ovalbumin-induced asthma mouse model. The inflammatory cell infiltration and MDA level of the lungs were reduced and SOD and CAT activity were increased by pterostilbene. The anti-inflammatory effects and alleviation of oxidative stress in the lungs of asthmatic mice were due to the activation of the AMPK/Sirt1 and Nrf2/HO-1 signaling pathways[74]. The activation of AMPK helps to ameliorate asthma due to the inhibition of airway smooth muscle cell proliferation[75]. The upregulation of Sirt1 is reported to reduce oxidative stress and lipid peroxidation in the lungs[76]. The activation of the Nrf2 signaling pathway that is responsible for anti-inflammatory and antioxidant effects in the lungs is crucial for preventing asthma[77]. Meanwhile, HO-1 can protect bronchial epithelial damage by reducing the release of IL-6 and IL-8[78]. Table 2 summarizes the potential of pterostilbene as an anti-inflammatory agent in various diseases and injuries in preclinical studies.

7. Conclusion

Pterostilbene can be an important natural compound in medicinal uses as it possesses greater advantages in terms of its pharmacokinetics with high bioavailability and better tissue distribution compared to resveratrol[79]. The anti-inflammatory activity of pterostilbene is one of the important pharmacological properties that could make pterostilbene a potential targeted anti-inflammatory therapeutic agent and prevent many inflammatory diseases including cancer[21]. Due to the vital function of NF-κB in regulating inflammation response, the molecular mechanisms that target the NF-κB signaling pathway in the treatment or prevention of inflammatory-related diseases can lead to the improvement and effectiveness of those therapeutic interventions[80]. Figure 2 summarizes the anti-inflammatory effects of pterostilbene *via* the NF-κB signaling pathway. In addition to the inflammation response, NF-κB also plays a vital role in other biological processes during cancer including cell cycle and cell death[81,82]. In addition, recent studies have reported that pterostilbene possesses many other health benefits including anti-microbial, anti-aging, and detoxification effects[83–85]. In conclusion, the present review shows that pterostilbene is a potential natural agent that can be developed as a therapeutic or preventive agent against various inflammatory-related diseases including cancer due to its potent anti-cancer and anti-inflammatory effects.

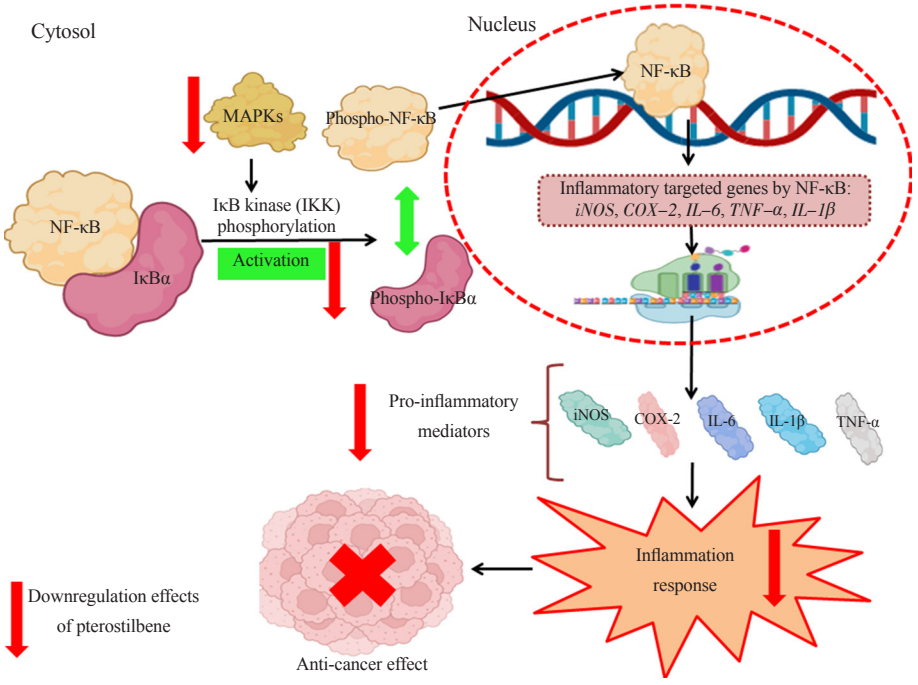

Figure 2. Pterostilbene downregulates the upstream and downstream effectors of the NF-κB signaling pathway to mitigate or prevent inflammation-related pathological conditions and exert anti-cancer effects (created with BioRender.com).

Conflict of interest statement

The authors declare no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

All authors contributed to the idea of this review. OS contributed to the draft and writing of this review. SFM and DFB contributed to the writing and proofreading. ARG contributed to the writing, proofreading, and funding acquisition.

References

[1] Hardman WE. Diet components can suppress inflammation and reduce cancer risk. *Nutr Res Pract* 2014; **8**(3): 233-240.

[2] Chan EWC, Wong CW, Tan YH, Foo JPY, Wong SK, Chan HT. Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties. *J Appl Pharm Sci* 2019; **9**(7): 124-129.

[3] Chatterjee K, Mukherjee S, Vanmanen J, Banerjee P, Fata JE. Dietary polyphenols, resveratrol and pterostilbene exhibit antitumor activity on an HPV E6-positive cervical cancer model: An *in vitro* and *in vivo* analysis. *Front Oncol* 2019; **9**: 352.

[4] Kim H, Seo KH, Yokoyama W. Chemistry of pterostilbene and its metabolic effects. *J Agric Food Chem* 2020; **68**(46): 12836-12841.

[5] Ghazali AR, Mahindran E, Ramalingam A, Chee L, Zainalabidin S. Protective effects of pterostilbene against cardiac oxidative stress and dysfunctionin nicotine-induced cardiac injury rat model. *Biomed Pharmacol J* 2021; **14**(2): 623-633.

[6] Spath E, Kromp K. Synthesis of pterostilbene. *Chem Ber B* 1941; **74**: 189-192.

[7] Dharmaraj V, Raj JS. Phytochemical profiling and GC-MS analysis of *Pterocarpus indicus* willd. using ethanolic stem bark and leaves extract. *Int J Bot Stud* 2021; **6**(1): 395-399.

[8] Thomson LAJ. *Pterocarpus indicus* (narra). Species profiles for pacific island agroforestry. [Online] Available from: https://raskisimani.files.wordpress.com/2013/01/pterocarpus-narra-legume-family.pdf [Accessed on 15 June 2023].

[9] Tsai HY, Ho CT, Chen YK. Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. *J Food Drug Anal* 2017; **25**(1): 134-147.

[10] Wang P, Sang S. Metabolism and pharmacokinetics of resveratrol and pterostilbene. *BioFactors* 2018; **44**(1): 16-25.

[11] Valletta A, Iozia LM, Leonelli F. Impact of environmental factors on stilbene biosynthesis. *Plants* 2021; **10**(1): 90.

[12] Paul S, Rimando AM, Hong JL, Ji Y, Reddy BS, Suh N. Anti-inflammatory action of pterostilbene is mediated through the p38 mitogen-activated protein kinase pathway in colon cancer cells. *Cancer Prev Res (Phila)* 2009; **2**(7): 650-657.

[13] Belviranli M, Okudan N. Well-known antioxidants and newcomers in sport nutrition: Coenzyme Q10, quercetin, resveratrol, pterostilbene, pycnogenol and astaxanthin. In: Manfred L (ed.). *Antioxidants in sport nutrition*. Boca Raton (FL): CRC Press/Taylor & Franci; 2015, p. 79-102.

[14] Kapetanovic IM, Muzzio M, Huang Z, Thompson TN, McCormick DL. Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. *Cancer Chemother Pharmacol* 2011; **68**(3): 593-601.

[15] Remsberg CM, Yáñez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM. Pharmacometrics of pterostilbene: Preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. *Phytother Res* 2008; **22**(2): 169-179.

[16] Shin HJ, Han JM, Choi YS, Jung HJ. Pterostilbene suppresses both cancer cells and cancer stem-like cells in cervical cancer with superior bioavailability to resveratrol. *Molecules* 2020; **25**(1): 228.

[17] Yeo SCM, Ho PC, Lin H. Pharmacokinetics of pterostilbene in Sprague-Dawley rats: The impacts of aqueous solubility, fasting, dose escalation, and dosing route on bioavailability. *Mol Nutr Food Res* 2013; **57**(6): 1015-1025.

[18] Ruiz MJ, Fernández M, Pico Y, Manes J, Asensi M, Carda C, et al. Dietary administration of high doses of pterostilbene and quercetin to mice is not toxic. *J Agric Food Chem* 2009; **57**(8): 3180-3186.

[19] Riche DM, McEwen CL, Riche KD, Sherman JJ, Wofford MR, Deschamp D, et al. Analysis of safety from a human clinical trial with pterostilbene. *J Toxicol* 2013; **2013**. doi: 10.1155/2013/463595.

[20] Choo QY, Yeo SCM, Ho PC, Tanaka Y, Lin HS. Pterostilbene surpassed resveratrol for anti-inflammatory application: Potency consideration and pharmacokinetics perspective. *J Funct Foods* 2014; **11**: 352-362.

[21] Lin WS, Leland JV, Ho CT, Pan MH. Occurrence, bioavailability, anti-inflammatory, and anticancer effects of pterostilbene. *J Agric Food Chem* 2020; **68**(46): 12788-12799.

[22] Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008; **454**(7203): 428-435.

[23]Heidland A, Klassen A, Rutkowski P, Bahner U. The contribution of Rudolf Virchow to the concept of inflammation: What is still of importance? *J Nephrol* 2006; **19**(Suppl 10): S102-S109.

[24]Libby P. Inflammatory mechanisms: The molecular basis of inflammation and disease. *Nutr Rev* 2007; **65**(3): S140-S146.

[25]Nathan C, Ding A. Nonresolving inflammation. *Cell* 2010; **140**(6): 871-882.

[26]Neurath MF. Resolution of inflammation: From basic concepts to clinical application. *Semin Immunopathol* 2019; **41**(6): 627-631.

[27]Hold GL, El-Omar ME. Genetic aspects of inflammation and cancer. *Biochem J* 2008; **410**(2): 225-235.

[28]Afify SM, Hassan G, Seno A, Seno M. Cancer-inducing niche: The force of chronic inflammation. *Br J Cancer* 2022; **127**(2): 193-201.

[29]Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, et al. New horizons in tumor microenvironment biology: Challenges and opportunities. *BMC Med* 2015; **13**(1): 1-14.

[30]Luster AD, Alon R, von Andrian UH. Immune cell migration in inflammation: Present and future therapeutic targets. *Nat Immunol* 2005; **6**(12): 1182-1190.

[31]Wang J, Li D, Cang H, Guo B. Crosstalk between cancer and immune cells: Role of tumor-associated macrophages in the tumor microenvironment. *Cancer Med* 2019; **8**(10): 4709-4721.

[32]Maeda H, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer. *Biochemistry (Mosc)* 1998; **63**(7): 854-865.

[33]Shaked H, Hofseth LJ, Chumanevich A, Chumanevich AA, Wang J, Wang Y, et al. Chronic epithelial NF-κB activation accelerates APC loss and intestinal tumor initiation through iNOS up-regulation. *PNAS* 2012; **109**(35): 14007-14012.

[34]Todoric J, Antonucci L, Karin M. Targeting inflammation in cancer prevention and therapy. *Cancer Prev Res (Phila)* 2016; **9**(12): 895-905.

[35]Dvorak HF. Tumors: Wounds that do not heal. *NEJM* 1986; **315**(26): 1650-1659.

[36]Trinchieri G. Inflammation in cancer: A therapeutic target? *Oncology* 2011; **25**(5): 418.

[37]Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420**(6917): 860-867.

[38]Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell* 2011; **144**(5): 646-674.

[39]Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, D'Alessandro N. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF-κB activation levels and in IAP gene expression. *Cancer Lett* 2005; **224**(1): 53-65.

[40]Ling J, Kang Y, Zhao R, Xia Q, Lee DF, Chang Z, et al. KrasG12D-induced IKK2/β/NF-κB activation by IL-1α and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. *Cancer Cell* 2012; **21**(1): 105-120.

[41]Kim C, Pasparakis M. Epidermal p65/NF-κB signalling is essential for skin carcinogenesis. *EMBO Mol Med* 2014; **6**(7): 970-983.

[42]Chen W, Li Z, Bai L, Lin Y. NF-kappaB in lung cancer, a carcinogenesis mediator and a prevention and therapy target. *Frontiers Biosci (Landmark Ed)* 2011; **16**(3): 1172-1185.

[43]Karin M, Greten FR. NF-κB: Linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol* 2005; **5**(10): 749-759.

[44]Brivanlou AH, Darnell Jr JE. Signal transduction and the control of gene expression. *Science* 2002; **295**(5556): 813-818.

[45]Chen ACH, Huang YY, Arany PR, Hamblin MR. Role of reactive oxygen species in low level light therapy. In: *Proceedings Volume 7165. Mechanisms for low-light therapy IV*. Bellingham, Washington USA: The International Society for Optical Engineering; 2009, p. 9-19.

[46]Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. *Signal Transduct Target Ther* 2017; **2**(1): 1-9.

[47]Chen F, Greene WC. Shaping the nuclear action of NF-κB. *Nat Rev Mol Cell Biol* 2004; **5**(5): 392-401.

[48]Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. *Mol Cancer* 2013; **12**(1): 1-15.

[49]Park MH, Hong JT. Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches. *Cells* 2016; **5**(2): 15.

[50]Bonizzi G, Karin M. The two NF-κB activation pathways and their role in innate and adaptive immunity. *Trends Immunol* 2004; **25**(6): 280-288.

[51]Sun SC. The non-canonical NF-κB pathway in immunity and inflammation. *Nat Rev Immunol* 2017; **17**(9): 545-558.

[52]Sun SC. Non-canonical NF-κB signaling pathway. *Cell Res* 2011; **21**(1): 71-85.

[53]Lin CW, Chou YE, Chiou HL, Chen MK, Yang WE, Hsieh MJ, et al. Pterostilbene suppresses oral cancer cell invasion by inhibiting MMP-2 expression. *Expert Opin Ther Targets* 2014; **18**(10): 1109-1120.

[54]Paul S, DeCastro AJ, Lee HJ, Smolarek AK, So JY, Simi B, et al. Dietary intake of pterostilbene, a constituent of blueberries, inhibits the β-catenin/p65 downstream signaling pathway and colon carcinogenesis in rats. *Carcinogenesis* 2010; **31**(7): 1272-1278.

[55]Zhang Y, Li Y, Sun C, Chen X, Han L, Wang T, et al. Effect of pterostilbene, a natural derivative of resveratrol, in the treatment of colorectal cancer through Top1/Tdp1-mediated DNA repair pathway. *Cancers (Basel)* 2021; **13**(16). doi: 10.3390/cancers13164002.

[56]Tan KT, Chen PW, Li S, Ke TM, Lin SH, Yang CC. 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.

[57]Surien O, Ghazali AR, Masre SF. Chemopreventive effects of pterostilbene through p53 and cell cycle in mouse lung of squamous cell carcinoma model. *Sci Rep* 2021; **11**(1): 1-11.

[58]Surien O, Ghazali AR, Masre SF. Histopathological effect of pterostilbene as chemoprevention in *N*-nitroso-tri-chloroethylurea (NTCU)-induced lung squamous cell carcinoma (SCC) mouse model. *Histol Histopathol* 2020; **35**(10): 1159-1170.

[59]Tong C, Wang Y, Li J, Cen W, Zhang W, Zhu Z, et al. Pterostilbene inhibits gallbladder cancer progression by suppressing the PI3K/Akt

pathway. *Sci Rep* 2021; **11**(1): 4391.

[60]Surien O, Masre SF, Basri DF, Ghazali AR. Chemopreventive effects of oral pterostilbene in multistage carcinogenesis of skin squamous cell carcinoma mouse model induced by DMBA/TPA. *Biomedicines* 2022; **10**(11): 2743.

[61]Wang D, Guo H, Yang H, Wang D, Gao P, Wei W. Pterostilbene, an active constituent of blueberries, suppresses proliferation potential of human cholangiocarcinoma *via* enhancing the autophagic flux. *Front Pharmacol* 2019; **10**. doi: 10.3389/fphar.2019.01238.

[62]Wawszczyk J, Jesse K, Kapral M. Pterostilbene-mediated inhibition of cell proliferation and cell death induction in amelanotic and melanotic melanoma. *Int J Mol Sci* 2023; **24**(2). doi: 10.3390/ijms24021115.

[63]Tsai ML, Lai C, Chen W, Ho C, Pan M. 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.

[64]Nikhil K, Sharan S, Roy P. A pterostilbene derivative suppresses osteoclastogenesis by regulating RANKL-mediated NFκB and MAPK signaling in RAW264. 7 cells. *Pharmaco Rep* 2015; **67**(6): 1264-1272.

[65]Xiong X, Lu W, Zhang K, Zhou W. Pterostilbene reduces endothelial cell apoptosis by regulation of the Nrf2 mediated TLR 4/MyD88/NF-κB pathway in a rat model of atherosclerosis. *Exp Ther Med* 2020; **20**(3): 2090-2098.

[66]Zeng Q, Lian W, Wang G, Qiu M, Lin L, Zeng R. Pterostilbene induces Nrf2/HO-1 and potentially regulates NF-κB and JNK-Akt/mTOR signaling in ischemic brain injury in neonatal rats. *3 Biotech* 2020; **10**(5): 1-16.

[67]Liu Z, Wang J, Zhang Y, Wu D, Li S, Jiang A, et al. Pterostilbene exerts hepatoprotective effects through ameliorating LPS/*D*-Gal-induced acute liver injury in mice. *Inflammation* 2021; **44**(2): 526-535.

[68]Yang H, Hua C, Yang X, Fan X, Song H, Peng L, et al. Pterostilbene prevents LPS-induced early pulmonary fibrosis by suppressing oxidative stress, inflammation and apoptosis *in vivo*. *Food Funct* 2020; **11**(5): 4471-4484.

[69]Zhang Y, Ren S, Ji Y, Liang Y. Pterostilbene ameliorates nephropathy injury in streptozotocin-induced diabetic rats. *Pharmacology* 2019; **104**(1-2): 71-80.

[70]Sun Y, Xu Y, Wang GN. Pterostilbene prevents intestinal ischemia reperfusion injury in Wistar rats *via* modulation of antioxidant defense and inflammation. *Trop J Pharm Res* 2015; **14**(8): 1383-1391.

[71]Amin A, Akhtar MF, Saleem A, Sharif A, Shah S, Khan MI, et al. Pterostilbene improves CFA-induced arthritis and peripheral neuropathy through modulation of oxidative stress, inflammatory cytokines and neurotransmitters in Wistar rats. *Inflammopharmacology* 2022; **30**(6): 2285-2300.

[72]Bangash Y, Saleem A, Akhtar MF, Anwar F, Akhtar B, Sharif A, et al. Pterostilbene reduces the progression of atopic dermatitis *via* modulating inflammatory and oxidative stress biomarkers in mice. *Inflammopharmacology* 2023; **31**(3): 1289-1303.

[73]Fan-Jiang PY, Lee PS, Nagabhushanam K, Ho CT, Pan MH. Pterostilbene attenuates high-fat diet and dextran sulfate sodium-induced colitis *via* suppressing inflammation and intestinal fibrosis in mice. *J Agric Food Chem* 2021; **69**(25): 7093-7103.

[74]Xu C, Song Y, Wang Z, Jiang J, Piao Y, Li L, et al. Pterostilbene suppresses oxidative stress and allergic airway inflammation through AMPK/Sirt1 and Nrf2/HO-1 pathways. *Immun Inflamm Dis* 2021; **9**(4): 1406-1417.

[75]Pan Y, Liu L, Li S, Wang K, Ke R, Shi W, et al. Activation of AMPK inhibits TGF-β1-induced airway smooth muscle cells proliferation and its potential mechanisms. *Sci Rep* 2018; **8**(1): 3624.

[76]Zhang Y, Li T, Pan M, Wang W, Huang W, Yuan Y, et al. SIRT1 prevents cigarette smoking-induced lung fibroblasts activation by regulating mitochondrial oxidative stress and lipid metabolism. *J Transl Med* 2022; **20**(1): 1-13.

[77]Rangasamy T, Guo J, Mitzner WA, Roman J, Singh A, Fryer AD, et al. Disruption of Nrf2 enhances susceptibility to severe airway inflammation and asthma in mice. *J Exp Med* 2005; **202**(1): 47-59.

[78]Zhang RG, Pan K, Hao Y, Yip CY, Ko WH. Anti-inflammatory action of HO-1/CO in human bronchial epithelium in response to cationic polypeptide challenge. *Mol Immunol* 2019; **105**: 205-212.

[79]Azzolini M, La Spina M, Mattarei A, Paradisi C, Zoratti M, Biasutto L. Pharmacokinetics and tissue distribution of pterostilbene in the rat. *Mol Nutr Food Res* 2014; **58**(11): 2122-2132.

[80]Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-κB pathway for the therapy of diseases: Mechanism and clinical study. *Signal Transduct Target Ther* 2020; **5**(1): 209.

[81]Ankers JM, Awais R, Jones NA, Boyd J, Ryan S, Adamson AD, et al. Dynamic NF-κB and E2F interactions control the priority and timing of inflammatory signalling and cell proliferation. *Elife* 2016; **5**: e10473.

[82]Kondylis V, Kumari S, Vlantis K, Pasparakis M. The interplay of IKK, NF-κB and RIPK 1 signaling in the regulation of cell death, tissue homeostasis and inflammation. *Immunol Rev* 2017; **277**(1): 113-127.

[83]Lee WX, Basri DF, Ghazali AR. Bactericidal effect of pterostilbene alone and in combination with gentamicin against human pathogenic bacteria. *Molecules* 2017; **22**(3): 463.

[84]Harun Z, Ghazali AR. 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.

[85]Majeed M, Majeed S, Jain R, Mundkur L, Rajalakshmi HR, Lad PS, et al. An open-label single-arm, monocentric study assessing the efficacy and safety of natural pterostilbene (*Pterocarpus marsupium*) for skin brightening and antiaging effects. *Clin Cosmet Investig Dermatol* 2020; **13**: 105-116.

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