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REVIEW

Parthenolide and Its Derivatives in the Treatment of Respiratory Tract Diseases: Therapeutic Effects and Molecular Mechanisms

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Abstract: Parthenolide (PTN), a sesquiterpene lactone derived from the medicinal plant feverfew (*Tanacetum parthenium)*, and its derivatives such as dimethylamino parthenolide (DMAPT) and dimethylaminomicheliolide fumarate (ACT001) exhibit distinguished anti-inflammatory, anticancer, antioxidant, and epigenetic activities, with accumulating evidence demonstrating their therapeutic potential in respiratory diseases. This review systematically summarizes the antitumor, anti-inflammatory, antioxidative, and anti-fibrotic effects of PTN and its derivatives in relevant animal models, elucidates the underlying pharmacological mechanisms involving STAT3, NF-κB, MAPK/ERK, and PI3K signaling pathways, and highlights recent advances in clinical applications and drug delivery strategies. A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus up to February 2026. Results demonstrate that PTN and its derivatives exert significant therapeutic effects in lung cancer, pulmonary fibrosis, asthma, pneumonia, and acute lung injury. We summarize the clinical translation progress of ACT001, including its safety and pharmacokinetic profiles, discuss emerging delivery systems such as micelles, and review the patent landscape of PTN derivatives. By integrating mechanistic insights with progress in clinical applications and drug delivery, this review provides a foundation for further mechanistic studies and supports the translational development of PTN-based therapies for respiratory disorders.

Keywords: parthenolide, DMAPT, ACT001, anti-inflammatory agents, respiratory tract diseases

Introduction

Parthenolide (PTN), a sesquiterpene lactone initially isolated from feverfew (*Tanacetum parthenium*), has been used for medicinal purposes for centuries in ancient Europe. Numerous derivatives have since been developed to enhance its pharmacological properties, most notably DMAPT and ACT001.[1] Accumulating evidence indicates that PTN and its derivatives possess potent anti-inflammatory, anticancer, and antioxidant activities.[2] In their comprehensive review, Freund et al highlighted the therapeutic potential of PTN and its derivatives across a spectrum of inflammatory and malignant diseases, including lung disorders, skin conditions, and hematological malignancies, while also elucidating their roles in modulating microtubule dynamics, epigenetic regulation, redox balance, and mitochondrial function.[3] Mechanistically, PTN and its derivatives exert their therapeutic effects primarily through inhibition of the NF-κB signaling pathway, a master regulator of inflammation and cell survival.[4–6] This mechanism underlies their beneficial effects in a range of respiratory diseases, including lung cancer, pulmonary fibrosis, and acute lung injury. However, the full spectrum of their therapeutic potential in respiratory disorders, as well as the optimal strategies for their clinical translation, has not been systematically reviewed.

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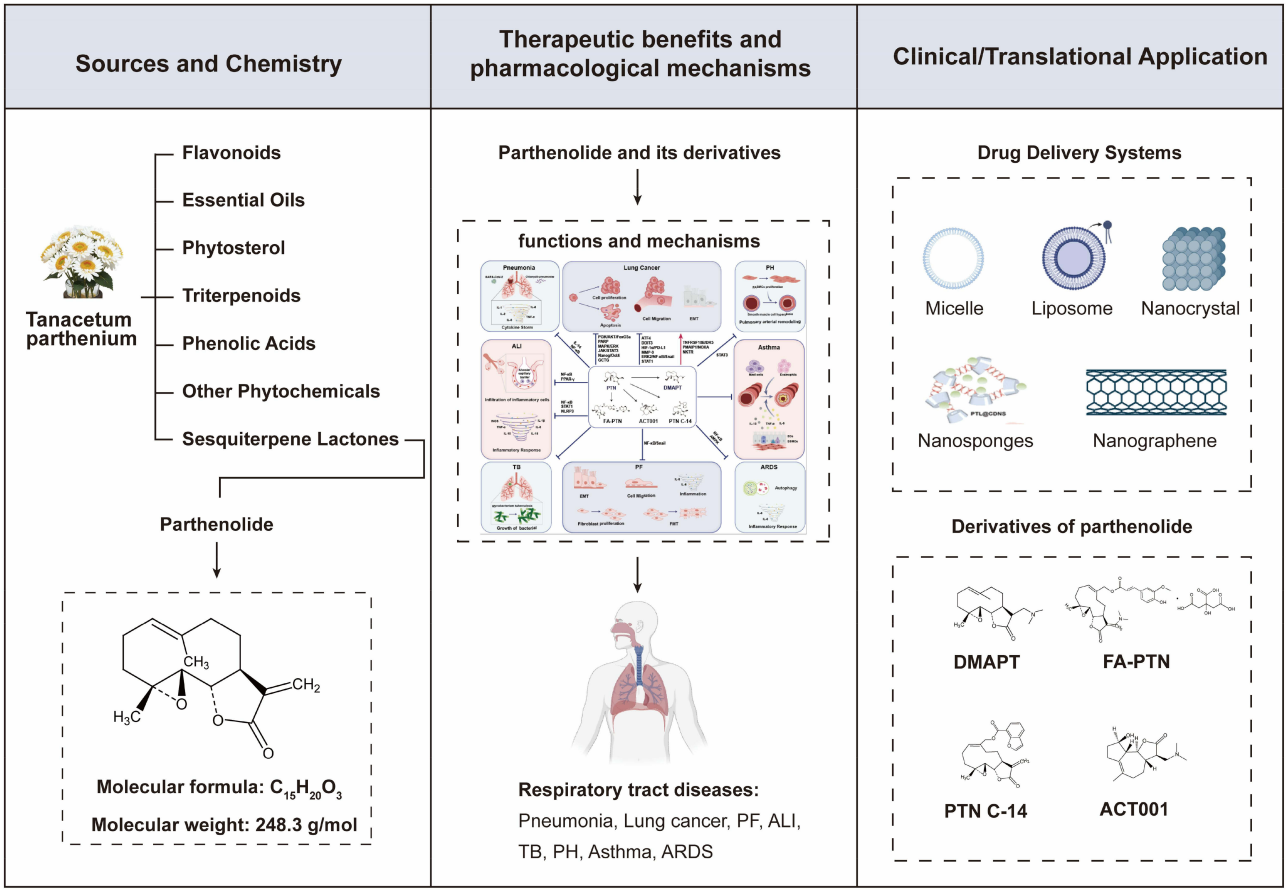
Graphical Abstract



Despite these promising pharmacological effects, the clinical translation of native PTN has been severely hampered by its poor aqueous solubility, metabolic instability, and suboptimal bioavailability. To overcome these limitations, two complementary strategies have been pursued: structural modification to generate more soluble derivatives, and the development of advanced drug delivery systems. DMAPT, an amine adduct of PTN, exhibits 100–1000-fold higher water solubility and up to 70% oral bioavailability, and has completed Phase I clinical trials.[7] ACT001, an orally available derivative with superior plasma stability, has advanced to Phase II/III clinical trials for lung cancer and interstitial lung diseases, demonstrating favorable safety profiles and preliminary efficacy. Concurrently, innovative delivery platforms—including liposomes, polymeric micelles, and nanoparticle-based formulations—have been engineered to enhance the pulmonary targeting and therapeutic index of PTN-based therapies.

In recent years, research reviews on parthenolide have progressively expanded in both scope and depth. Beginning with a comprehensive overview of its chemical synthesis and biological activities, the focus gradually shifted to structural modification strategies targeting its anticancer properties and multi-target antitumor mechanisms.[2,3,8] The scope subsequently extended to its therapeutic potential in skeletal diseases and cytokine storms, culminating in a systematic preclinical summary in hematological malignancies.[9,10] Existing studies either concentrate on cancers or emphasize skeletal/inflammatory diseases. The review on tumor bone diseases and the review on hematological malignancies did not explore other derivatives or drug delivery content.[9,10] Some reviews did not address the therapeutic effects or clinical translation of the compounds.[3,11] Another oncology review, while discussing derivatives, only mentioned DMAPT and omitted the important derivative ACT001.[2] The review on drug delivery also did not cover its

derivatives.[11] These comparisons clearly demonstrate that our review is more comprehensive to date, encompassing respiratory diseases, including drug delivery and the two important derivatives DMAPT and ACT001, while incorporating the latest literature up to February 2026.

Materials and Methods

A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus using keywords related to parthenolide, its derivatives, and respiratory diseases. All relevant articles published up to February 2026 were considered. The keywords were searched individually and in combination within the title and abstracts. The following terms were used: parthenolide, DMAPT, ACT001, chronic respiratory diseases, lung, respiratory disease, toxicity, pulmonary diseases. Articles that were tangentially related to PTN and its derivatives were excluded. Reviews, case reports, editorials, books, posters, and conference abstracts were excluded from the review. The flowchart of the literature search and screening process is illustrated in Figure 1.

Overview of Parthenolide

Sources of Parthenolide and Its Derivatives

Tanacetum parthenium (L). Sch.Bip., commonly known as feverfew, is a perennial medicinal herb belonging to the Asteraceae (the daisy/aster family). It is also referred to as featherfew, a vernacular name derived from its finely dissected, feather-like leaf morphology. T. parthenium is native to the Balkan Peninsula in southeastern Europe. Currently, it is widely distributed across Europe, East Asia (eg, China and Japan), North Africa, North America, and Australia. In North America, it was first introduced in the mid-19th century, and has now become naturalized from eastern Canada south to Maryland, and westward to Missouri in the United States. It occurs primarily in open, well-lit habitats including roadsides, fields, wastelands, and forest edges. T. parthenium is a low-growing, bushy, strongly aromatic perennial herb, with a mature height ranging from 0.3 to

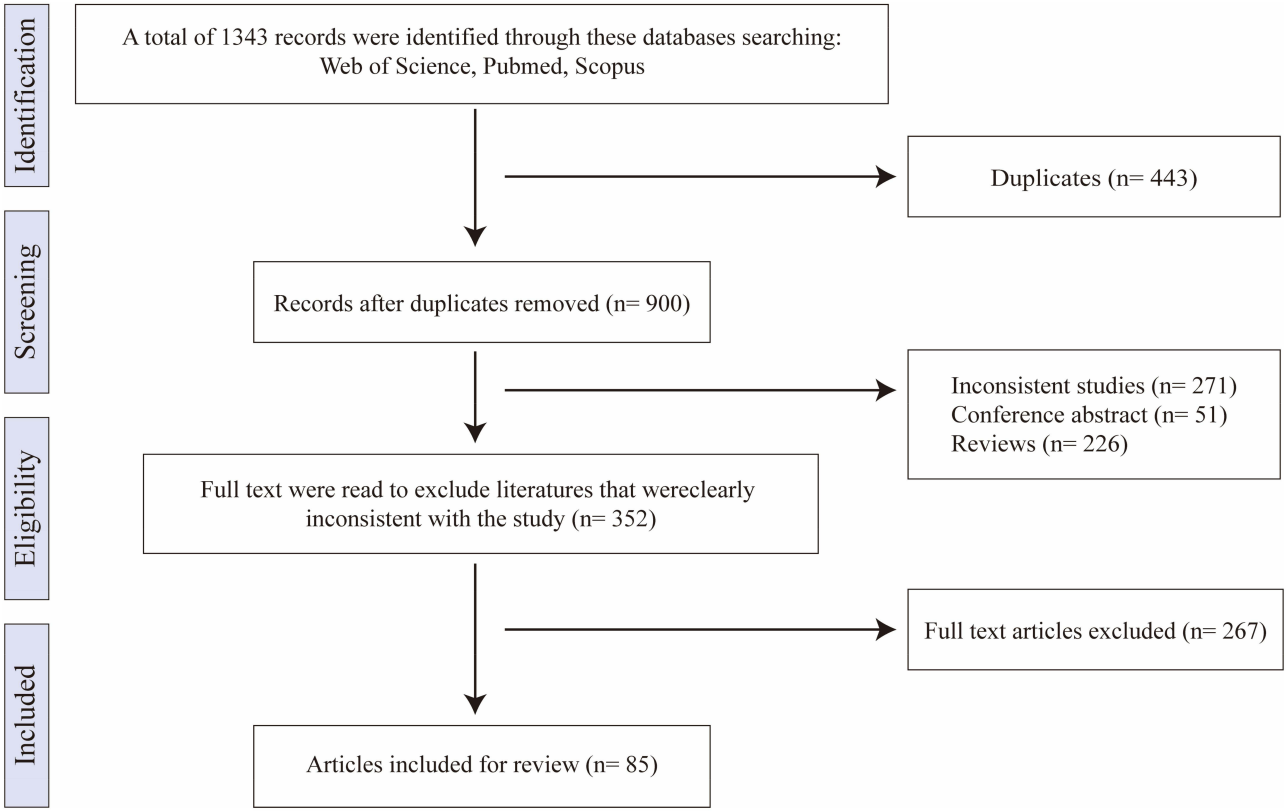


Figure 1 The flow diagram of the study selection for the review. The original search supplied 900 articles for screening, the majority of which were excluded after reviewing the title and abstract. The remaining articles were accessed through full-text review and finally included 85 studies.

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1 m. The whole plant produces a distinctive pungent, bitter aromatic scent, and forms a dense clumped shrubby habit via erect, well-branched stems. The leaves are alternate, yellow-green, and usually no longer than 8 cm, with a pinnate to bipinnate lamina resembling chrysanthemum leaves, slightly recurved margins, and a subglabrous surface with sparse short hairs restricted to veins and petioles. Flowering occurs mainly from July to October in temperate regions of the Northern Hemisphere. The daisy-like capitula, approximately 2 cm in diameter, are borne in dense flat-topped corymbose clusters at the apices of stems.[12,13] Each capitulum comprises a compact central disc of bright yellow tubular florets, encircled by a single whorl of white ray florets; this inflorescence structure is morphologically very similar to that of German chamomile (*Matricaria chamomilla L*). Feverfew (*Tanacetum parthenium*) was used for treatment of fever, migraine headaches, stomach aches and other diseases in a long history of Greece and Europe.[13] A variety of metabolites have been identified in different parts of the feverfew. Among these, the most thoroughly investigated class of phytochemicals includes Sesquiterpene Lactones, to which parthenolide belongs. In addition, compounds such as flavonoids, phytosterol, essential oils, Triterpenoids, Phenolic Acids and Other phytochemicals are also present in feverfew (Supplement Table 1).

PTN is the major active constituent found in the shoots, flowers, and leaves of *Tanacetum parthenium*, while the PTN used for research today is mainly isolated from the leaves of *Chrysanthemum parthenium* with 97% purity.[14] PTN is also the secondary metabolite of the Asteraceae/Compositae and Magnoliaceae families. To our knowledge, PTN and its derivatives have been reported to have anti-inflammatory and anti-tumor properties.[9,15,16] In previous studies, PTN was specifically cytotoxic to cancer cells but not to normal cells.[17–20] In addition, the poor pharmacological properties of PTN have limited its clinical use. Therefore, scientists designed and synthesized a derivative of PTN, DMAPT, which is formed by aza-Michael addition to α-exo-methylene-γ-butyrolactone (αMγB), an amine adduct of PTN. DMAPT has 100–1000 times higher aqueous solubility than PTN and up to 70% oral bioavailability.[7] However, the biological activity and efficacy of DMAPT were lower than that of PTN.[21,22] At present, DMAPT has been tested in clinical trials.[23] In addition, the epoxidized derivatives of the C1–C10 alkene of parthenolide could inhibit the growth of cancer cells.[24] The C7 epimer 65 of parthenolide was also less cytotoxic than PTN.[25] Furthermore, ACT001, an oral derivative of parthenolide, has the fumarate salt form of dimethylaminomicheliolide (DMAMCL) and is more stable in the plasma.[26] The highly potent pharmacological properties of ACT001 allow the drug to be explored in a growing number of inflammatory and proliferative diseases, such as lung cancer, lung injury and so on.[27–32] In addition to the above derivatives, there are other derivatives of PTN involved in the pathological process of respiratory diseases, which are described below.

Chemistry of Parthenolide and Its Derivatives

PTN is a germacrane sesquiterpene lactone compound, with the molecular formula of $C_{15}H_{20}O_3$ and a molecular weight of 248.3 g/mol (Figure 2A). Parthenolide is a white powder with moderate activity, low chemical/metabolic stability, and low water solubility resulting from an annulated trans αMγB and a trisubstituted epoxide.[20,33–35] The molecular formula of DMAPT is $C_{17}H_{27}NO_3$ and the molecular weight of DMAPT is 293.4 g/mol (Figure 2B). Although DMAPT is white powder, the aqueous solubility of DMAPT (1.1 mg/mL at 40 °C in water) is higher than that of PTN (0.67 mg/mL at ultrasound in water) due to the amine.[7] The molecular formula of ACT001 is $C_{17}H_{27}NO_3$ and the molecular weight is 293.4 g/mol (Figure 2C). In general, PTN, DMAPT and ACT001 have high solubility in dimethylsulfoxide (DMSO). To improve the anti-tumor activity of PTN, Yanhong Zhou et al modified the C-14 position of PTN and synthesized a series of parthenolide C-14 derivatives (PTN C-14). As one of the PTN C-14, the molecular formula of compound ZA-5 was $C_{24}H_{24}O_6$. It was a white solid with the best anti-proliferative activity (Figure 2D).[36] Ferulic acid (FA) is a natural phenolic acid with anti-inflammatory properties. PTN was combined with FA to produce several PTN derivatives, termed ferulic acid -Parthenolide (FA-PTN). Of these derivatives, compound 6 is the most water soluble, and its chemical structural formula is $C_{27}H_{36}NO_7$ (Figure 2E).[37]

Safety and Toxicity of Parthenolide and Its Derivatives

For the use of PTN and its derivatives in humans, many researchers have paid considerable attention to the safety and toxicity of PTN and its derivatives. In vitro studies have shown that PTN has anticancer properties in various cancers. The IC50 of PTN was 5 to 20 μM in tumorigenic cell lines. In addition, concentrations of PTN above 30 μM showed cytotoxicity in human macrophages.[38] Interestingly, PTN is more specific cytotoxic to cancer cells than normal cells.

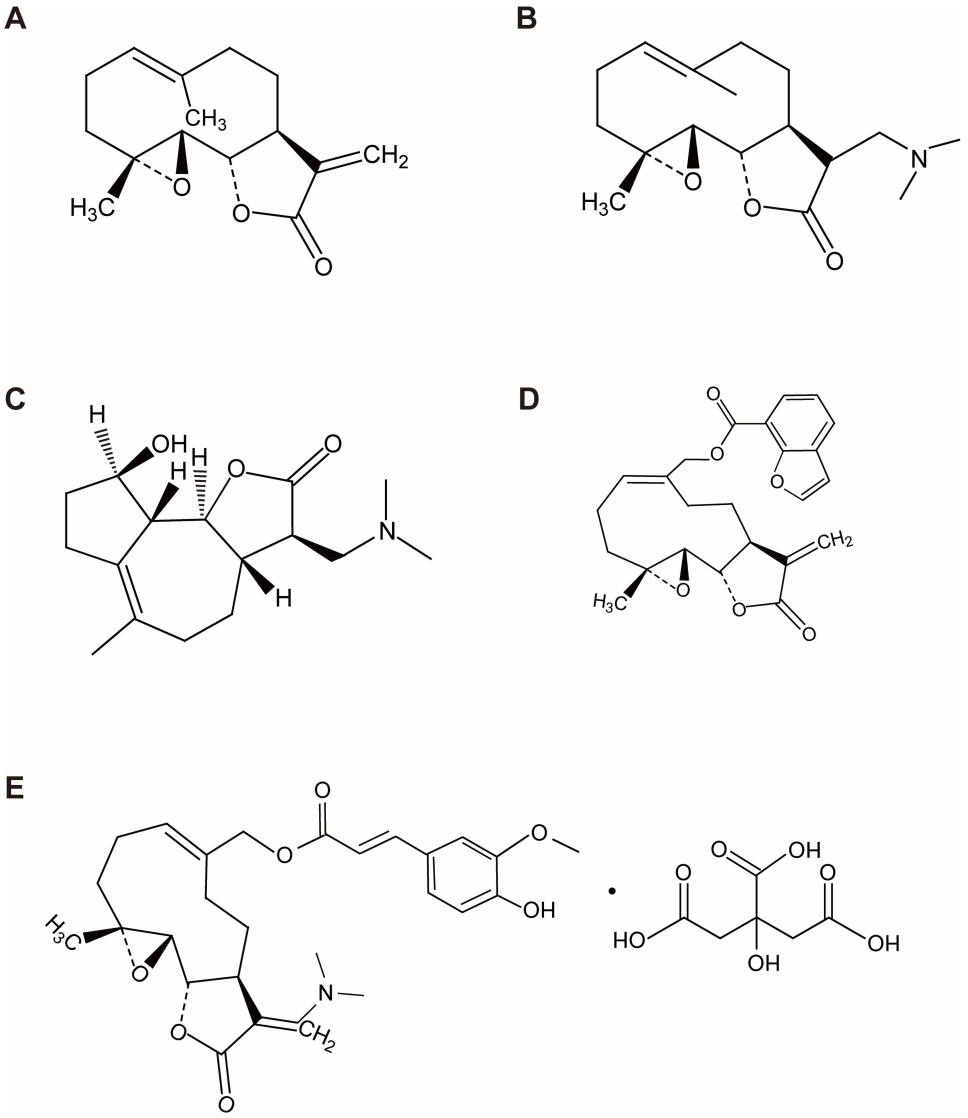

Figure 2 Chemical structure of parthenolide and its derivatives. (**A**) The 2D structure of Parthenolide (PTN); (**B**) The 2D structure of DMAPT; (**C**) The 2D structure of ACT001; (**D**) The 2D structure of PTN C-14 ZA-5. (**E**) The 2D structure of FA-PTN compound 6.

After treatment with 5 μM PTN, the viability of leukemia stem cells was reduced by 90%, whereas that of normal stem cells was reduced by <15%.[17] 20 μM DMAPT could inhibit the proliferation of lung cancer cells. Notably, the first phase I clinical trial with PTN to evaluate its pharmacokinetic properties and toxicity was explored in 2004, it showed that 4 mg/kg PTN orally administered could not be toxic.[39] The first clinical trial using DMAPT in patients with leukemia was initiated in 2007.[7] Currently, ACT001 has been tested in 10 clinical trials around the world, most of which are Phase II clinical trials.

The Therapeutic Benefits and Pharmacological Mechanisms of Parthenolide and Its Derivatives in Respiratory Tract Diseases

A large body of research has demonstrated that PTN and its derivatives provide protection and treatment for a range of respiratory tract diseases. Notably, their therapeutic mechanisms operate through a number of different signaling pathways. We have summarized the detailed experimental model, pharmacological effect, and mechanism of parthenolide and its derivatives in respiratory tract diseases are listed in Tables 1 and 2.

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Table 1 The Therapeutic Benefits and Pharmacological Mechanisms of Parthenolide and Its Derivatives in Respiratory Tract Diseases

Drug	Diseases	Experimental model	Pharmacological Effect	Mechanism	References
Parthenolide	Lung cancer	NSCLC cells: A549 cells; human medulloblastoma (TE671); human colon adenocarcinoma (HT-29); HUVECs.	Inhibited proliferation of cells	/	[40]
Parthenolide	Lung cancer	NSCLC cells: PGCL3 cells.	Inhibited proliferation of PGCL3 cells	Inhibited NF-κB/upA pathway.	[41]
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549, A549-T24 cells, H460 cells; SCLC cells: NCI-H446 cells;	Inhibited proliferation and induced apoptosis of cells; attenuated mitochondrial apoptosis signaling cascade.	Inhibited NF-κB pathway.	[42]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Inhibited proliferation of cells	Regulated the miR-107/NF-κB pathway.	[43]
Parthenolide	Lung cancer	Transplanted tumor female mice model; NSCLC cells: A549 and H460 cells; SCLC cells: NCI-H446 cells; A549LLC	Reduced cell viability; inhibited migration and invasion of cancer cells; attenuated EMT of cancer cells.	Regulated the ERK2/NF-κB/ Snail pathway	[44]
Parthenolide	Lung cancer	EGFR mutant NSCLC cell line H1975	Inhibited proliferation, migration and invasion of cancer cells and induced apoptosis of cancer cells.	Inhibit p-AKT; regulated the expression of downstream target proteins Bcl-2, Bax, caspase-3, HIF-1α and MMP-9.	[45]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Inhibited cell proliferation, migration and colony formation and induced cell apoptosis.	Up-regulation of p53 and down-regulation of c-myc expression; activated PARP, caspase-9 and caspase-3 apoptotic pathways.	[46]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Improved thermal sensitivity of cells and induced cell apoptosis.	Inhibited NF-κB pathway in a p53- and hsp72-independent manner.	[47]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Reduced cell viability; induce cell apoptosis; regulated cell cycle of cells.	Downregulated Bcl-2/ Bax mRNA ratio.	[48]
Parthenolide	Lung cancer	Transplanted tumor SCID mice model; NSCLC cells: A549 cells	Induced cells apoptosis; enhanced ROS levels.	/	[49]
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549 cells, A549-T24 cells; SCLC cells: NCI-H446 cells.	Induced apoptosis of cancer cells.	Inhibited NF-κB pathway.	[5]
Parthenolide	Lung cancer	NSCLC cells: A549 cells, A549-T24 cells; SCLC cells: NCI-H446 cells.	Induced cell apoptosis; attenuated downstream mitochondrial apoptosis signaling cascade.	Inhibited NF-κB pathway.	[50]
Parthenolide	Lung cancer	NSCLC cells: A549 cells, H157 cells.	Induced apoptosis and cell cycle arrest; triggered stronger ER stress response.	Upregulated TNFRSF10B and downregulated CFLAR; increased the expression of PMAIP1 and decreased the level of MCL1.	[51]

(*Continued*)

Table 1 (Continued).

Drug	Diseases	Experimental model	Pharmacological Effect	Mechanism	References
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549 and H1299 cells.	Inhibited proliferation and migration of cancer cells.	Inhibited IGF-1R/PI3K/AKT pathway.	[52]
Parthenolide	Lung cancer	NSCLC cells: GLC-82 cells.	Inhibited cell proliferation and migration; induced cell apoptosis.	Regulated B-Raf/MAPK/Erk and STAT3 pathways.	[53]
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: H1975, PC-9, HCC827, H358, H460, A549 cells; The human normal lung epithelial BEAS-2B cells.	Inhibited the growth of NSCLC cells.	Suppressed EGFR/MAPK/ERK and PI3K/Akt pathways.	[54]
Parthenolide	Lung cancer	NSCLC cells: A549 and H526 cells.	Inhibited cell proliferation and angiogenesis of cancer; induced cell apoptosis.	Downregulated the expression of Bcl-2 and upregulated the expression of E2F1, P53, GADD45, BAX, BIM, and CASP 3,7,8,9.	[55]
Parthenolide	Lung cancer	NSCLC cells: A549 cells; A549/DOX cells.	Induced cell apoptosis.	Attenuated P-gp expression, NF-κB activation and HSP70 upregulation.	[56]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Inhibited cell proliferation and induced cell apoptosis.	Inhibited NF-κB pathway.	[57]
Parthenolide	Lung cancer	NSCLC cells: A549 cells.	Induced cell apoptosis and cell cycle arrest in G2/M of A549 cells.	Inhibited NF-κB pathway.	[58]
Parthenolide	Lung cancer	Transplanted tumor mice model; H2030BrM, PC9BrM, SIM-A9, HMC3, LL/2 cells, microglia	Blocked M2 polarization.	Suppressed the activation of JAK2/STAT3 pathway.	[59]
Parthenolide	Lung cancer	NSCLC cells: A549 cells, A549-T24 cells.	Sensitized the cancer cells and enhanced cytotoxic response of cancer cells via mitochondria-dependent death pathway and the caspase-independent death pathway.	Mixed micelles loaded with paclitaxel and parthenolide	[60]
Parthenolide	Lung cancer	NSCLC cells: A549 cells, A549-T24 cells.	Reduced cancer cell viability.	EGF conjugated mixed micelles loaded with paclitaxel and parthenolide	[61]
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549 cells.	Inhibited migration and induced mitochondrial dysfunction of cells; impaired ROS generation, decreased the MMP, caused abnormal perinuclear clustering of cytochrome c and $Ca2^{+}$.	CK/parthenolide tLyp-1 Liposomes	[62]
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549 cells.	Inhibited growth and migration of A549 cells.	The cocktail liposome system: betulinic acid, parthenolide, honokiol and ginsenoside Rh2 were loaded into liposome systems	[63]

(*Continued*)

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Table 1 (Continued).

Drug	Diseases	Experimental model	Pharmacological Effect	Mechanism	References
Parthenolide	Lung cancer	Transplanted tumor nude mice model; NSCLC cells: A549 cells; HUVEC	Suppressed cell proliferation, migration, and invasion; inhibited HUVEC tube formation; inhibited A549 xenograft tumor growth	Inhibited PD-L1 synthesis through mTOR/p70S6K/4EBP1/eIF4E and RAS/RAF/MEK/MAPK signaling pathways and promoted PD-L1 protein degradation through the lysosomal pathway	[64]
Parthenolide	Lung cancer	H1975 LUAD cells; quantitative proteomics (LC-MS/MS); In vivo: xenograft in nude mice.	Reduces proliferation, induces apoptosis, increases ROS; inhibits tumor growth in vivo.	Bound to GCTG and inhibited the expression of GCTG protein	[65]
Parthenolide	Lung cancer	LLC cells; In vivo: LLC xenograft mice model	Enhances CTX-induced cytotoxicity and apoptosis; reduces tumor growth, decreases angiogenesis (CD31), and modulates tumor microenvironment	Reduced p-NF-κB p65 and nuclear translocation	[66]
ACT001	Lung cancer	In vitro: NSCLC cell lines (H1299, H1975); In vivo: LLC xenograft mice model	Inhibits cell proliferation, migration, invasion, and induces G1/S phase arrest. Suppresses tumor growth.	Inhibited STAT1/STAT3 pathway	[67]
ACT001	Lung cancer	In vitro: SCLC cell lines (NCI-H1688, NCI-H446), THP-1 macrophages; In vivo: NCI-H1688 xenograft and metastasis models in nude mice	Inhibited cell proliferation, invasion, migration, and colony formation. Reduces glucose consumption and lactate production. Suppresses tumor growth and metastasis in vivo. Reduces M2 macrophage polarization and increases M1 macrophages in the TME.	Binds to PGK1 and inhibits PGK1 enzymatic activity and its S203 phosphorylation,	[68]
ACT001	Lung cancer	In vitro: A549, NCI-H820 In vivo: Subcutaneous xenograft (NCI-H820 in BALB/c nude mice), Pulmonary metastasis model (tail vein injection of NCI-H820-luci cells)	Inhibited cell proliferation and migration. Suppressed tumor growth, Reduced pulmonary metastasis	Directly bound to Olig2 protein, Induced Olig2 ubiquitination and proteasomal degradation	[28]
ACT001	Lung cancer	In vitro: H1703, H1975, EBC-1, H226, PC9, LTEP-A2, HCC827 In vivo: H1703 subcutaneous xenograft in BALB/c nude mice	Inhibited cell proliferation, Suppressed tumor growth,	Upregulated NKTR expression, Inhibited AKT phosphorylation	[33]
DMAPT	Lung cancer	In vitro: A549, H522, BEAS2B In vivo: A549 and UMUC-3 cells xenograft mice model	Inhibited cell proliferation, induced apoptosis, Suppresses tumor growth	Induced phosphorylation of c-JUN, Increased total JNK and p-JNK, inhibited NF-κB DNA binding	[69]
DMAPT	Lung cancer	In vitro: NSCLC cells: A549 cells and H1299 cells; In vivo: NNK induced cancer	Inhibited proliferation of cells; enhanced X-ray induced cell killing;	Inhibited NF-κB and DNA double-strand break repair	[70]

(*Continued*)

Table 1 (Continued).

Drug	Diseases	Experimental model	Pharmacological Effect	Mechanism	References
DMAPT	Lung cancer	In vitro: Immortalized BEAS-2B and its premalignant (1799 and 1198) and malignant (1170); In vivo: subcutaneous injection induced cancer	Inhibited proliferation of cells; induced concentration-dependent apoptotic activities;	Induced the DNA binding activity of STAT3; decreased the expression of Mcl-1, cyclin D1, Survivin, p-Akt and IKK-β; increased the expression of p-ERK	[71]
Parthenolide	PF	In vivo: bleomycin induced PF mice model; In vitro: TGF-β1 induced A549 cells and primary AECs; PPF isolated from NaCl/BLM-treated mice and HFL1 cell lines	Inhibited the viability and migration of cells, attenuated EMT of cells	Inhibited the NF-κB/Snail pathway.	[6]
ACT001	PF	Bleomycin induced PF mice model; Paraquat induced PF mice model	Ameliorated PF mice model; Attenuated EMT process of mice	Inhibited NF-κB pathway	[72]
ACT001	IPF	FBS/TGF-β1 induced Primary lung fibroblasts derived from eight patients with IPF and eight age-matched (NDC.	Inhibited fibroblast proliferation; reduced FMT; reduced fibronectin deposition.	Inhibited NF-κB pathway	[31]
Parthenolide	PH	Hypoxia-induced rat model; Hypoxia-induced PASMCs	Inhibited the proliferation and migration of PASMCs and induced the apoptosis of PASMCs	Inhibited STAT3 pathway	[73]
Parthenolide	ALI	TNF-α induced A549 cells.	Restrained the activation of IL-8	Inhibited NF-κB pathway	[74]
Parthenolide	ALI	LPS induced ALI mice model; LPS induced A549 cells, BEAS-2B cells and alveolar macrophage MH-S cells.	Suppressed infiltration of inflammatory cells, airway permeability and production of pro-inflammatory cytokines.	Inhibited NF-κB pathway	[4]
Parthenolide	CF	LPS induced CF mice model; TNF/IL-1β induced AS/S cells, IB3/S9 cells.	Inhibited inflammatory response	Inhibited NF-κB pathway	[75]
FA-Parthenolide	ALI	Bleomycin induced ALI mice model; LPS induced RAW264.7 cells	Mitigated the inflammation of mice and cells	/	[38]
ACT001	ALI	LPS induced ALI mice model; LPS induced RAW264.7 cells	Ameliorated ALI mice model; Promoted M2 polarization and inhibited M1 polarization of RAW264.7 cells; Suppressed inflammation and oxidative stress.	Inhibited NF-κB pathway; Inhibited STAT1 pathway	[30]
ACT001	ALI	LPS-induced rat alveolar macrophage line NR8383	Inhibited cell viability; reduced the expression and release of inflammatory factors, attenuated cell pyroptosis.	Inhibited NLRP3/caspase-1 sign- aling pathway Inhibited PPAR-γ/NF-κB signaling	[29]

(*Continued*)

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Table 1 (Continued).

Drug	Diseases	Experimental model	Pharmacological Effect	Mechanism	References
ACT001	ALI	In vitro: BMDMs. In vivo: LPS-induced ALI mouse model	Improves survival, reduced body weight loss, alleviates lung histopathological damage, reduced inflammasome activation	Binds to NLRP3 protein. Inhibits DRP1	[76]
ACT001	ALI	In vitro: RAW264.7 In vivo: LPS induced ALI mice model	Promoted M2 polarization and inhibited M1 polarization of RAW264.7 cells; Improves survival, alleviates lung histopathological damage, reduced inflammasome activation	Inhibited STAT1/CIITA/MHC-IIsignaling pathway	[77]
ACT001	RILI	20 Gy X-ray chest irradiation induced RILI	Inhibited cell oxidative stress; alleviates radiation-induced inflammatory and fibrotic alterations; attenuated radiation- induced pyroptosis	Inhibited NLRP3/Caspase-1 pathway	[32]
Parthenolide	Tuberculosis	*Mycobacterium tuberculosis and M avium*	Inhibited growth of bacteria	/	[78]
Synthesized compounds of parthenolide	Tuberculosis	*Mycobacterium tuberculosis and S. aureus*	Inhibited growth of bacteria	Regioselective and Stereoselective Synthesis of Parthenolide Analogs by Acyl Nitroso-Ene Reaction	[34]
ACT001	ARDS	CLP induced ARDS rat model.	Alleviated inflammation and induced autophagy activity in ARDS rat model.	Regulated MAPK and NF-κB pathways	[79]
Parthenolide	Pneumoniae	Human monocytic cell line Mono Mac 6; infection with C. pneumoniae strain TW-183 (MOI 5)	Induced apoptosis of cells	Inhibited NF-κB expression	[80]
Parthenolide	Asthma	Ovalbumin-induced chronic asthma in BALB/c mice	Reduced subepithelial smooth muscle thickness, Decreased epithelial thickness	Decreased IL-4 levels	[81]

Note: Blank cells indicate that the mechanism of action was not reported in the original reference cited.

Effects of Parthenolide and Its Derivatives in Lung Cancer

Lung cancer is considered the leading cause of cancer death worldwide.[82] Based on histological assessment, the main categories of lung cancer include non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mesothelioma, sarcoma, and carcinoid. Lung adenocarcinoma (LUAD), as the most common pathological subtype of NSCLC, represents a significant healthcare burden.[83] Although the development of molecularly targeted therapies and immune checkpoint inhibitors (ICIs) has moderately improved the overall survival (OS) of patients with lung cancer, the five-year survival rate of patients was only 21%.[84,85] There is substantial evidence to support the claim that PTN and its derivatives, in combination with other drugs and materials, may suppress the development of lung cancer.[36,40,41,86] However, the underlying mechanism by which PTN and its derivatives exert their anti-cancer effects remains to be fully elucidated.

Recent studies have shown that PTN can induce apoptosis of lung cancer cells and inhibit the growth of human lung cancer cells.[5,40–43,45–58,86] Several studies showed that PTN inhibited proliferation and induced apoptosis by inhibiting the NF-κB pathway.[5,40–42,63] In other researches, the mechanism of anti-proliferation effect of PTN was to inhibit p-AKT and to regulate the expression of downstream target proteins Bcl-2, Bax, caspase-3, HIF-1α and MMP-9.[43] PTN could inhibit the

Table 2 Summary of the Data About Dose and Effects of Combination Treatment with Parthenolide and Its Derivatives in vivo

Drug	Diseases	Animal Model	Dose	Duration	Administration Approach	Result	References
Parthenolide	Lung cancer	Intratracheal injection induced cancer	5 mg/kg three times weekly	4 weeks	Intraperitoneal injection	Life span↑ RelA/NF-κB↓ phosphorylated I-κBα↓ nuclear translocation of NF-κB p65↓	[42]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	8 mg/kg 16 mg/kg	25 days	Intraperitoneal injection	Tumor volume↓ median survival time↑ shifted stoves↓ p-ERK 2↓ NF-κB↓ Snail↓	[44]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	20 mg/kg three times weekly	4 weeks	Intraperitoneal injection	Tumor volume↓ RelA/NF-κB↓ nuclear translocation of NF-κB p65↓	[5]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	2 mg/kg	72 hours	Tail vein injection	Apoptosis↑	[49]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	10 mg/kg/d	24 days	Intraperitoneal injection	Tumor weight and volume↓	[52]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	20 mg/kg/d	14 days	Intraperitoneal injection	Tumor weight and volume↓ p-ERK↓ p-AKT↓ Cleaved Caspase-3↑ Ki-67↓	[54]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	7.5 mg/kg/3 days	15 days	Intraperitoneal injection	Tumor volume↓	[62]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	20.5 mg/kg/3 days	27 days	Intravenous injection	Tumor volume↓ Ki-67↓	[63]
Parthenolide	Lung cancer	Intracranial implantation induced cancer	1 mg/kg/3 days	40 days	Intraperitoneal injection	Tumor metastasis↓ M2 microglia polarization↓ *Arg1* promoter activity↓ Iba1+/CD206+ cells (M2) ↓ Iba1+/CD11b+ cells (M1) ↑ CCL20↓ p-JAK2↓ p-STAT3↓	[59]
Parthenolide	Lung cancer	Subcutaneous injection induced cancer	25 mg/kg/3 days 50 mg/kg/3 days	30 days	Oral administration	Tumor volume↓ HIF-1α ↓ PD-L1 ↓	[64]
Parthenolide	Lung cancer	H1975 subcutaneous xenograft in BALB/c nude mice	20 mg/kg/3 day	4 weeks	Intraperitoneal injection	Tumor weight and volume ↓ amino acid metabolic reprogramming↓ GCTG ↓	[65]
Parthenolide	Lung cancer	LLC subcutaneous xenograft in C57BL/6 mice	40 mg/kg/day	21 days	Oral administration	Tumor growth rate ↓ angiogenesis ↓ TGF-β ↓ α-SMA ↓	[66]
ACT001	Lung cancer	LLC subcutaneous xenograft in C57BL/6 mice	400 mg/kg/day	28 days	Oral administration	Tumor sizes and weights ↓	[67]
ACT001	Lung cancer	NCI-H1688 subcutaneous xenograft in nude mice; GFP-H1688 tail vein metastasis model	200 mg/kg/day	21 days	Oral administration	Tumor volumes and tumor weights ↓ p-PDHK1 ↓	[68]
DMAPT	Lung cancer	Subcutaneous injection induced cancer	50 mg/kg/d 100 mg/kg/d 100 mg/kg/bid	48 days	Oral administration	Tumor volume↓ TRAF-2↓ nuclear p21↑	[69]

(*Continued*)

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Table 2 (Continued).

Drug	Diseases	Animal Model	Dose	Duration	Administration Approach	Result	References
DMAPT	Lung cancer	NNK induced cancer	10 mg/kg twice weekly	13 weeks	Intranasal instillations	Tumor volume↓ p-STAT3↓ Mcl-1↓	[70]
DMAPT	Lung cancer	Subcutaneous injection induced cancer	100 mg/kg/d	7 days	Oral administration	Tumor growth rate↓	[71]
ACT001	Lung cancer	Subcutaneous injection induced cancer	100 mg/kg/3 days	21 days	Oral administration	Tumor volume and tumor weight ↓ Olig2 ↓ CD133↓ Nanog ↓ and Oct4↓	[28]
ACT001	Lung cancer	Subcutaneous injection induced cancer	200 mg/kg/d	12 days	Oral administration	Growth of tumors↓ Ki67↓ NKTR↓ p-AKT↓	[33]
Parthenolide	Asthma	Ovalbumin induced asthma	3 mg/kg/d	7 days	Aerosol inhalation	Basal membrane thickness↓ subepithelial smooth muscle thickness↓ epithelial thickness↓ IL-4↓	[81]
Parthenolide	PF	Bleomycin induced PF	12.5mg/kg/d 25 mg/kg/d 50 mg/kg/d	4 weeks	Intragastric administration	Body weight loss↓ collagen content and deposition↓ Col1, α-SMA and vimentin↓ E-cad, MMP1↑ the lung coefficient↓ inspiratory resistance↓ expiratory resistance↓ dynamic compliance↑ macrophages, lymphocytes, neutrophils↓ infiltration of inflammatory cells, edema, thrombosis, and structure destruction↓ TGF-β, TNF-α and IL-4↓ NF-κB↓ Snail↓	[6]
ACT001	PF	Bleomycin induced PF; Paraquat induced PF	12.5mg/kg/d 25 mg/kg/d 50 mg/kg/d	4 weeks	Intragastric administration	Body weight loss↓ the lung coefficient↓ HYP and collagen content↓ infiltration of inflammatory cells, edema and structure destruction↓ TGF-β1 and TNF-α↓ IFN-γ↑ E-cad, MMP1↑ Vimentin↓	[72]
Parthenolide	PH	Hypoxia-induced PH	10mg/kg 30mg/kg every other day	3 weeks	Intraperitoneal injection	Mean pulmonary arterial pressure↓ pulmonary vascular remodeling↓ right ventricular hypertrophy↓ p-STAT3↓	[73]

(*Continued*)

Table 2 (Continued).

Drug	Diseases	Animal Model	Dose	Duration	Administration Approach	Result	References
Parthenolide	ALI	LPS induced ALI	5 mg/kg 10 mg/kg	1 h 24 h	Intraperitoneal injection	Infiltration of inflammatory cells around respiratory tract↓ MPO↓ W/D ratio↓ total protein concentration in BALF↓ total cell number in BALF↓ IL-1β, TNF-α和IL-6↓	[4]
FA-Parthenolide	ALI	Bleomycin induced ALI	10 mg/kg/d	14 days	Intraperitoneal injection	Body weight loss↓ inflammatory cell infiltration and edema in lung tissue↓	[38]
ACT001	ALI	LPS induced ALI	100 mg/kg/d 200 mg/kg/d	3 days	Intraperitoneal injection	Percent survival↑ Temperature stability↑ infiltration of inflammatory cells and alveolar structure destruction↓ lung injury scores↓ W/D ratio↓ neutrophils and protein in BALF↓ TNF-α and IL-6↓	[77]
ACT001	ALI	LPS induced ALI	200 mg/kg 1 h prior to LPS instillation.	24 hours	Intratracheal instillation	Infiltration of pulmonary M1 macrophages↓ TNF-α1↓, IL-1β↓, BALF↓ p-IKKβ↓ p-IκB ↓ p-p65 ↓ p-STAT1	[30]
ACT001	ALI	LPS-induced ALI	100 mg/kg 200 mg/kg 2 h before the LPS challenge	7 days	Intratracheal instillation	Body weight loss ↓, BALF ↓ IL-1β ↓ Nlrp3 ↓	[76]
ACT001	RILI	20 Gy X-ray chest irradiation induced RILI	50 mg/kg/d 100 mg/kg/d 200 mg/kg	67days	Intragastric administration	Pro-inflammatory cytokine release and fibrosis↓ NLRP3↓ ASC↓ Caspase-1 Pro-Caspase-1↓ GSDMD-N↓	[32]
Parthenolide	CF	LPS induced CF	3 mg/kg 1 h prior to LPS instillation.	8 hours	Intraperitoneal injection	Mean percent BAL PMNs↓ mean total PMN/mL BAL↓ TNF-α↓ MIP-2↓ KC↓ the degradation of IκBα↓ NF-κB↓	[75]
ACT001	ARDS	CLP induced ARDS	50 mg/kg/d 100 mg/kg/d	48h	Oral administration	Survival rate↑ lung D/W ratio↑ TNF-α, IL-6和IL-1β↓ p-AMPK↑ p-mTOR↓ Beclin1↑ LC3B II↑ p-IκBα↓ p-p65↓	[79]

Notes: upward arrows (↑) indicate increased expression or activity, and downward arrows (↓) indicate decreased expression or inhibition.

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proliferation, migration, and colony formation of A549 cells by upregulating p53 and downregulating c-myc expression and activating PARP signaling pathway. M. Lin et al found that PTN inhibited cell proliferation by regulating the MAPK/ERK pathway and suppressing STAT3 activity.[52] In addition, PTN inhibited the growth of NSCLC cells by suppressing the phosphorylation of EGFR and its downstream pathways MAPK/ERK, PI3K/AKT.[53] PTN also induced apoptosis by increasing apoptotic pathways, such as upregulation of caspase-9 and caspase-3, downregulation of Bcl-2/Bax mRNA ratio or microenvironment is important for cancer development, PTN was found to block nicotine-induced M2 polarization by decreasing activation of the JAK2/STAT3 pathway.[44–46,54] Xiaofei Zhao et al found that PTN induced apoptosis and cell cycle arrest in human lung cancer cells through tumor necrosis factor receptor/ death receptor 5 (TNFRSF10B/DR5) and PMAIP1/ NOXA which were associated with extrinsic apoptosis.[50] Knockdown TNFRSF10B or PMAIP1 (intrinsic signaling pathway) or overexpression of CFLAR/c-FLIP (extrinsic apoptotic pathway) protects cells from PTN-induced apoptosis. In addition, PTN induces apoptosis through increasing the expression levels of endoplasmic reticulum (ER) stress markers (ATF4, DDIT3, ERN1, HSPA5, p-EIF2A). Knockdown of ATF4 and DDIT3 inhibited PTN-induced apoptosis. In A549/shCDH1 cells, the downregulation of CFLAR and MCL1 by PTN was more significant than in control cells, while ATF4, DDIT3, TNFRSF10B, and PMAIP1 were significantly upregulated.[50] Longhua Sun et al found that PTN could significantly inhibit the proliferation and migration of A549 and H1299 cell lines. In addition, PTN was able to inhibit the growth of lung cancer in mouse models of subcutaneous xenografting. The underlying mechanism may be the ability of PTN to block phosphorylation of insulin-like growth factor 1 receptors (IGF-1R), and IGF-1-induced phosphorylation of AKT and FoxO3α.[51] PTN inhibited PD-L1 expression by suppressing HIF-1α and RAS Interaction. PTN Inhibits HIF-1α by the mTOR/p70S6K/4EBP1/eIF4E Signaling Pathway. Besides, PTN inhibited PD-L1 synthesis via RAS/RAF/MEK/MAPK pathways while promoting PD-L1 degradation through the lysosomal pathway, thereby enhancing T cell-mediated tumor killing and suppressing tumor growth in non-small cell lung cancer.[59] Through drug sensitivity prediction analysis, parthenolide may have therapeutic potential for LCaMPS low-risk lung adenocarcinoma patients.[64] Parthenolide alters amino acid metabolism and induces oxidative stress in LUAD cells by targeting γ- glutamyltransferase (GCTG, also known as GGCT), thereby inhibiting tumor growth.[87] Parthenolide synergizes with low-dose cyclophosphamide (metronomic chemotherapy) in lung cancer by inhibiting NF-κB, improving survival and reducing tumor growth in vitro and in vivo.[65]

Up to 40% of lung cancer patients develop brain metastasis, and the median survival of these patients remains less than 6 months. PTN not only have direct tumor suppressive activity, but also inhibit cancer metastasis. Low-dose (<1μM) PTN suppressed lung cancer brain metastasis by blocking nicotine-induced M2 microglia polarization.[44] In the treatment of lung cancer, tumor cells could rapidly become chemoresistant. PTN had synergistic effects with vorinostat (suberoylanilide hydroxamic acid, SAHA) in inhibiting proliferation of A549 cells.[45]

DMAPT could inhibit cell proliferation and induce apoptosis by generating ROS, activating c-Jun N-terminal kinase (JNK) and inhibiting the NF-κB pathway in A549 and H522 cells.[66] Neil C. Estabrook et al found DMAPT inhibited X-ray-induced cell proliferation, sublethal split-dose repair and DNA double-strand break repair by decreasing constitutive NF-κB binding activity in A549 and H1299 cells, while DMAPT inhibited X-ray-induced tumor growth in nude mice.[69] DMAPT inhibited cell viability, induced apoptosis of cancer cells and persistence of DNA damage by inhibiting IκBα phosphorylation and abrogating NF-κB response to ionizing radiation, further inhibited NF-κB-mediated expression of BRCA1, FANCD2 and RAD51 which are biomarkers of HR protein activity, and inhibited auto-phosphorylation of DNA-PK complex to suppress NHEJ pathway in A549, H460 and H1299 cells.[71] In 1799 cells, 1198 cells and 1170 cell lines, DMAPT inhibited lung tumorigenesis via suppression of STAT3 activation and expression of Mcl-1.[70]

ACT001 concentration-dependently inhibited cell proliferation and migration, in addition, ACT001 reduced tumorsphere formation. In vivo and vitro experiments verified the mechanism of ACT001 function which was directly bind to Olig2 and induce Olig2 ubiquitination (Ub) degradation to decrease CD133 transcription.[27] ACT001 inhibited cell proliferation and migration; induced G1/S arrest in the NSCLC cell lines by increasing NKTR expression and inhibiting AKT phosphorylation.[32] The IC50 values of the antiproliferative activities of the PTN derivatives (ZA-1 ~ ZA-13) were better than PTN.[36] ACT001 inhibits NSCLC progression and enhances T cell-mediated immunity by directly binding to STAT1 and STAT3, suppressing phosphorylation of STAT1 and STAT3, and subsequently downregulating PD-L1 expression.[88] ACT001 suppresses SCLC progression by covalently binding to PGK1 at Cys316, inhibiting its activity and lactate production, which in turn reduces M2 macrophage polarization and enhances anti-tumor immunity.[67]

In summary, parthenolide and its derivatives have been most extensively and thoroughly studied in the context of lung cancer to date. We have summarized the above content and illustrated the mechanisms in Figure 3.

Effects of Parthenolide and Its Derivatives in Asthma

Asthma is mostly characterized by airway hyper reactivity (AHR), airway inflammation and airway remodeling induced by non-specific airway stimulation, involving a variety of cells such as airway epithelial cells, eosinophils and mast cells.[68] Bronchial smooth muscle (BSM) cells are effector cells of bronchoconstriction that can produce inflammatory mediators and angiogenic factors.[89] Z Arıkan-Ayyıldız et al showed that PTN administration ameliorated part of the pathological changes in the ovalbumin-induced asthma mouse model. The thickness of epithelial cells and BSM cells was lower in the parthenolide group than in the placebo group. However, parthenolide alone is not as efficient as dexamethasone therapy, and the combination of parthenolide and dexamethasone did not add any beneficial effect to dexamethasone treatment.[90] At present, no preclinical or clinical studies have been conducted on other parthenolide derivatives in asthma. The effects and mechanisms of parthenolide in asthma are still unclear and need further investigation.

Effects of Parthenolide and Its Derivatives in Pulmonary Fibrosis

Pulmonary fibrosis (PF), particularly idiopathic pulmonary fibrosis (IPF), is a chronic multifactorial lung disease with destroyed alveolar architecture and altered extracellular matrix.[81] The pathogenesis of IPF is complex, but no effective treatment is currently available. In recent years, the mortality rate of PF has increased significantly, seriously threatening

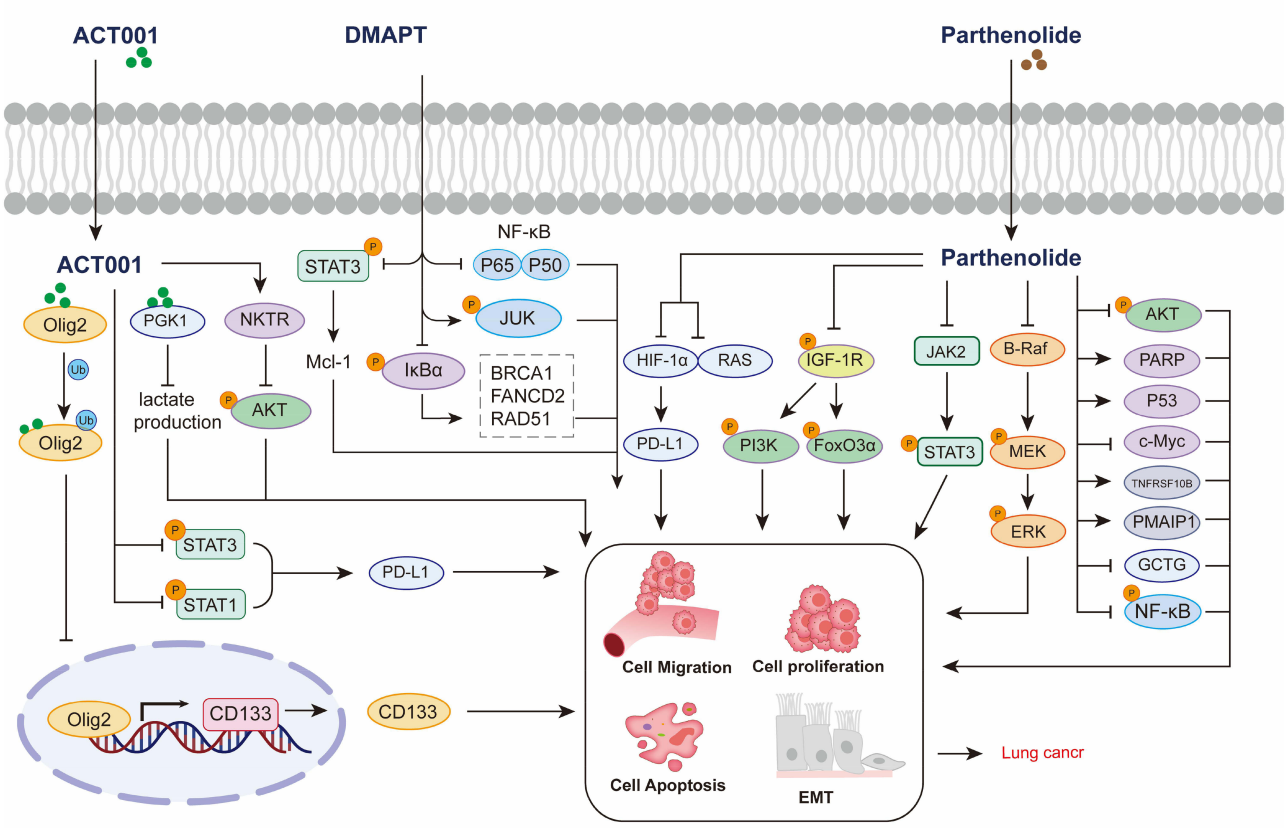

Figure 3 Molecular mechanisms of PTN and its derivatives in Lung cancer. Parthenolide and its derivatives showed therapeutic role for lung cancer by inhibiting cell proliferation, migration and epithelial-to-mesenchymal transition (EMT) of lung cancer cells, inducing apoptosis. PTN inhibits lung cancer cell proliferation and induces apoptosis by suppressing NF-κB, AKT, MAPK/Erk, EGFR, JAK2/STAT3, and IGF-1R pathways, while upregulating p53 and activating extrinsic apoptosis via TNFRSF10B/DR5. PTN also enhances anti-tumor immunity by promoting lysosomal PD-L1 degradation and suppressing HIF-1α-mediated PD-L1 synthesis. DMAPT induces apoptosis through JNK activation, inhibits NF-κB-mediated DNA repair by suppressing BRCA1, FANCD2, and RAD51 expression, and blocks STAT3 activation and Mcl-1 expression. ACT001 directly binds to Olig2, inducing its degradation to decrease CD133 transcription; increases NKTR expression to inhibit AKT phosphorylation and induce G1/S arrest; binds to STAT1/STAT3 to downregulate PD-L1 and enhance T cell immunity; and covalently binds to PGK1 to inhibit lactate production and reduce M2 macrophage polarization. Collectively, these mechanisms inhibit proliferation, migration, and tumor growth while promoting apoptosis and anti-tumor immunity.

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human health.[91] Xiao-He Li et al found that PTN reduced the cell viability and migration rate of lung fibroblasts and inhibited the expression of epithelial-to-mesenchymal transition (EMT) related transcription factors in alveolar epithelial cells. In addition, PTN could attenuate bleomycin-induced pulmonary fibrosis in a mice model by inhibiting the NF-κB/Snail signaling pathway.[6] One of the PTN derivatives, ACT001, was further investigated. ACT001 inhibited the proliferation of primary lung fibroblasts from IPF patients. By testing α-SMA and fibronectin levels, ACT001 was shown to reduced fibroblast-to-myofibroblast transition (FMT) and fibronectin deposition of fibroblasts.[30] ACT001 ameliorated bleomycin-induced PF mice model and the paraquat-induced PF mice model by inhibiting the NF-κB pathway.[92]

In summary, ACT001 and parthenolide currently play a role in the treatment of pulmonary fibrosis, and the mechanism is illustrated in Figure 4.

Effects of Parthenolide and Its Derivatives in Pulmonary Hypertension

Pulmonary hypertension (PH) is a chronic pulmonary disease characterized by pulmonary arterial remodeling and resulting in right ventricular (RV) failure and death. Prolonged hypoxia or underlying lung diseases, leading to pulmonary vascular endothelial cell dysfunction and abnormal proliferation of pulmonary artery smooth muscle cells (PASMCs). These pathological changes ultimately result in pulmonary vascular remodeling and elevated pulmonary artery pressure.[72] In hypoxia-induced rat PH model, PTN could significantly alleviate hypoxia-induced pulmonary artery hypertension and pulmonary arterial remodeling. PTN inhibited the proliferation and migration of PASMCs and induced the apoptosis of PASMCs. Furthermore, PTN could directly interact with STAT3 and markedly inhibited STAT3 phosphorylation and nuclear translocation. PTN suppressed STAT3-targeted genes involved in cell cycle progression (Cyclin D1) and anti-apoptosis (Bcl-2), thereby inhibiting PASMC proliferation and promoting apoptosis.[93] (Figure 5). Currently, there are no clinical data available regarding the use of PTN and its derivatives in pulmonary hypertension.

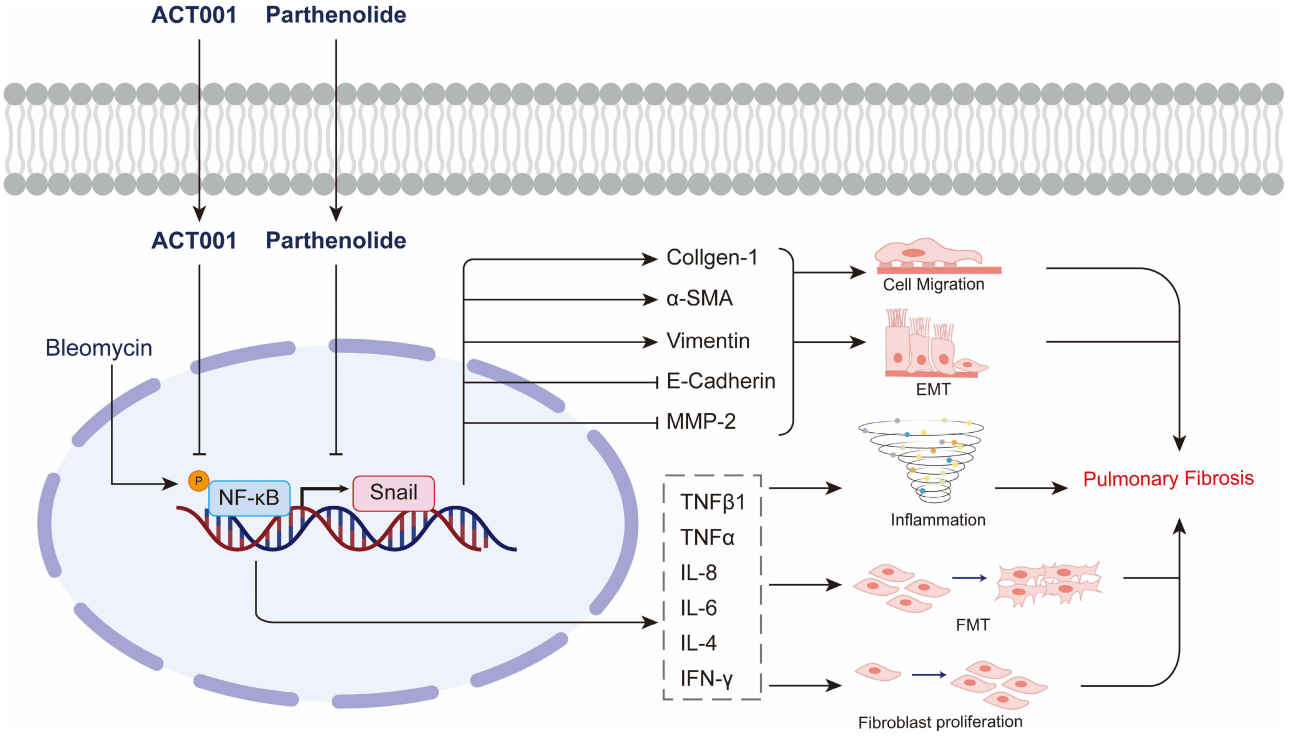

Figure 4 Molecular mechanisms of PTN and its derivatives in pulmonary fibrosis. Parthenolide (PTN) and ACT001 attenuate pulmonary fibrosis through inhibition of the NF-κB/Snail signaling pathway. PTN reduces lung fibroblast viability and migration, suppresses EMT-related transcription factors, and decreases inflammatory cytokines and mesenchymal markers (Collagen-1, α-SMA, Vimentin, MMP-2) while restoring E-cadherin. ACT001 inhibits fibroblast-to-myofibroblast transition (FMT), reducing α-SMA and fibronectin deposition, and ameliorates bleomycin- and paraquat-induced pulmonary fibrosis in mouse models. Collectively, both compounds exert anti-fibrotic effects by suppressing inflammation, EMT, FMT, and extracellular matrix deposition.

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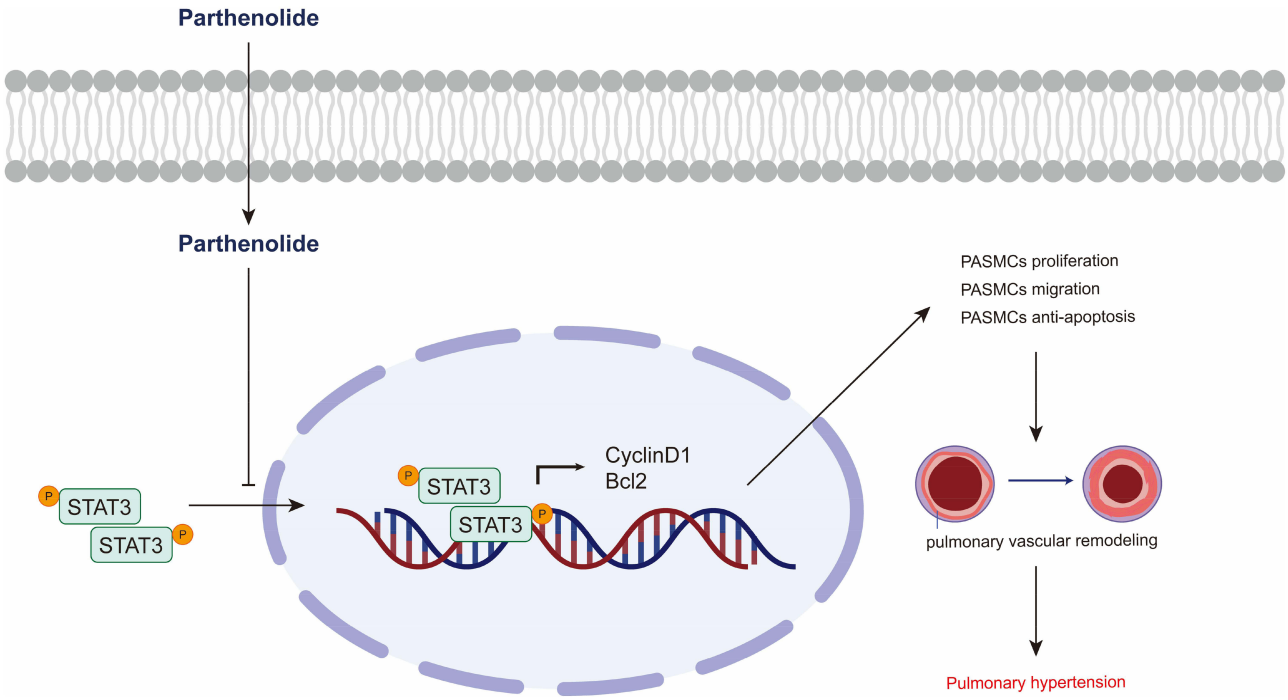

Figure 5 Molecular mechanisms of PTN and its derivatives in pulmonary hypertension. PTN alleviates pulmonary hypertension by targeting STAT3 signaling in pulmonary artery smooth muscle cells. PTN directly interacts with STAT3 and inhibits its phosphorylation and nuclear translocation, thereby suppressing the expression of STAT3-targeted genes involved in cell cycle progression (Cyclin D1) and anti-apoptosis (Bcl-2). This leads to inhibition of PASMC proliferation and migration, induction of PASMC apoptosis, and subsequent reduction of pulmonary vascular remodeling.

Effects of Parthenolide and Its Derivatives in Acute Lung Injury

Acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), involving an excessive inflammatory response in lung tissue, are the leading causes of acute respiratory failure.[73] The primary pathophysiology of acute lung injury is the recruitment of pro-inflammatory mediators and the activation of excessive neutrophils. ALI is also associated with injury to endothelial-alveolar epithelial tissue, disruption of the alveolar-capillary barrier, increased pulmonary vascular permeability, impaired gas exchange and interstitial edema.[94] Patients always have many clinical comorbidities, including sepsis, pneumonia, infection and multiple transfusions. However, there are no effective treatments for acute lung injury. PTN was found to restrain IL-8 activation by inhibiting the NF-κB pathway.[95] In the LPS-induced ALI mice model, PTN suppressed inflammatory cells infiltration, airway permeability and pro-inflammatory cytokines production, and reduced LPS-induced NF-κB phosphorylation, which is the key regulatory transcription factor in ALI. Furthermore, PTN also inhibited the inflammatory response in LPS-induced cystic fibrosis (CF) mice model associated with IkappaB kinase.[74] Parthenolide inhibits excessive IL-8 production in CF epithelial cells by targeting both NF-κB and MAPK/AP-1 signaling pathways, with differential effects on mRNA stability.[75] In bleomycin-induced ALI mice model, ferulic acid parthenolide (FA-PTN) mitigated inflammation in mice and cells.[37]

ACT001 inhibited cell viability, reduced the expression and release of inflammatory factors and attenuated cell pyroptosis by inhibiting NLRP3/caspase-1 pathway and PPAR-γ/NF-κB signaling.[28] ACT001 attenuates LPS-induced acute lung injury by inhibiting NLRP3 inflammasome-dependent pyroptosis, partly through regulating the mitochondrial fission protein DRP1.[96] Hui Guo et al found that ACT001 was protective against LPS-induced ALI mice model. ACT001 promoted M2 polarization and inhibited M1 polarization of RAW264.7 cells, while suppressing inflammation and oxidative stress.[29] ACT001 inhibited p-IKKβ (Ser176/180) and p-STAT1 (Tyr701), and overexpression of IKKβ and STAT1 could enhance ACT001-induced downregulation of M1 polarization.[29] ACT001 alleviates sepsis-induced ALI by exerting anti-inflammatory and antioxidative activity via inhibiting the STAT1/CIITA/MHC-II pathway, thereby improving mouse survival, reducing lung inflammation, and promoting RAW264.7 cell polarization to an anti-inflammatory phenotype.[76] Furthermore, in the chest x-ray irradiation induced radiation-induced lung injury (RILI) model, ACT001

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attenuated radiation-induced inflammation and fibrosis. ACT001 inhibited inflammatory cytokines (TNF-α, TGF-β1, IL-1β, IL-6) and cellular oxidative stress (MDA, SOD and GSH levels). ACT001 specifically reduced pyroptosis by inhibiting the pyroptosis-associated protein NLRP3.[31] ACT001 mediated autophagy and inflammation in ARDS through the AMPK and NF-κB pathways in the cecum ligation puncture (CLP)-induced ARDS rat model.[77] In summary, ACT001, parthenolide (PTN), and FA-PTN currently play a role in inhibiting inflammation in acute lung injury, and the mechanism is illustrated in Figure 6.

Effects of Parthenolide and Its Derivatives in Tuberculosis

Tuberculosis (TB) is a high morbidity infectious disease caused mainly by *Mycobacterium tuberculosis*. Early stage of TB is difficult to diagnose and treat. The REMA assay showed that PTN inhibited the growth of *Mycobacterium tuberculosis*.[79] Bruna Gioia et al synthesized a series of PTN analogues by acyl nitroso-ene reaction. Some of the compounds were inactive against M. tuberculosis, while others showed greater inhibitory activity.[33] Current evidence for parthenolide and its derivatives in tuberculosis is limited to preliminary in vitro findings, and no mechanistic or clinical studies have been reported to date.

Effects of Parthenolide and Its Derivatives in Pneumonia

Pneumonia is a multi-pathogenic disease characterized by fever, cough, pleurisy, dyspnoea and increased sputum production.[78] At present, pneumonia is the leading cause of respiratory death for the coronavirus disease 2019 (COVID-19), which is spreading rapidly around the world.[97] Mohsen Bahrami et al found that patients with COVID-19 have a state of hyperinflammation or a cytokine storm. IL-6 plays a key role in the cytokine storm

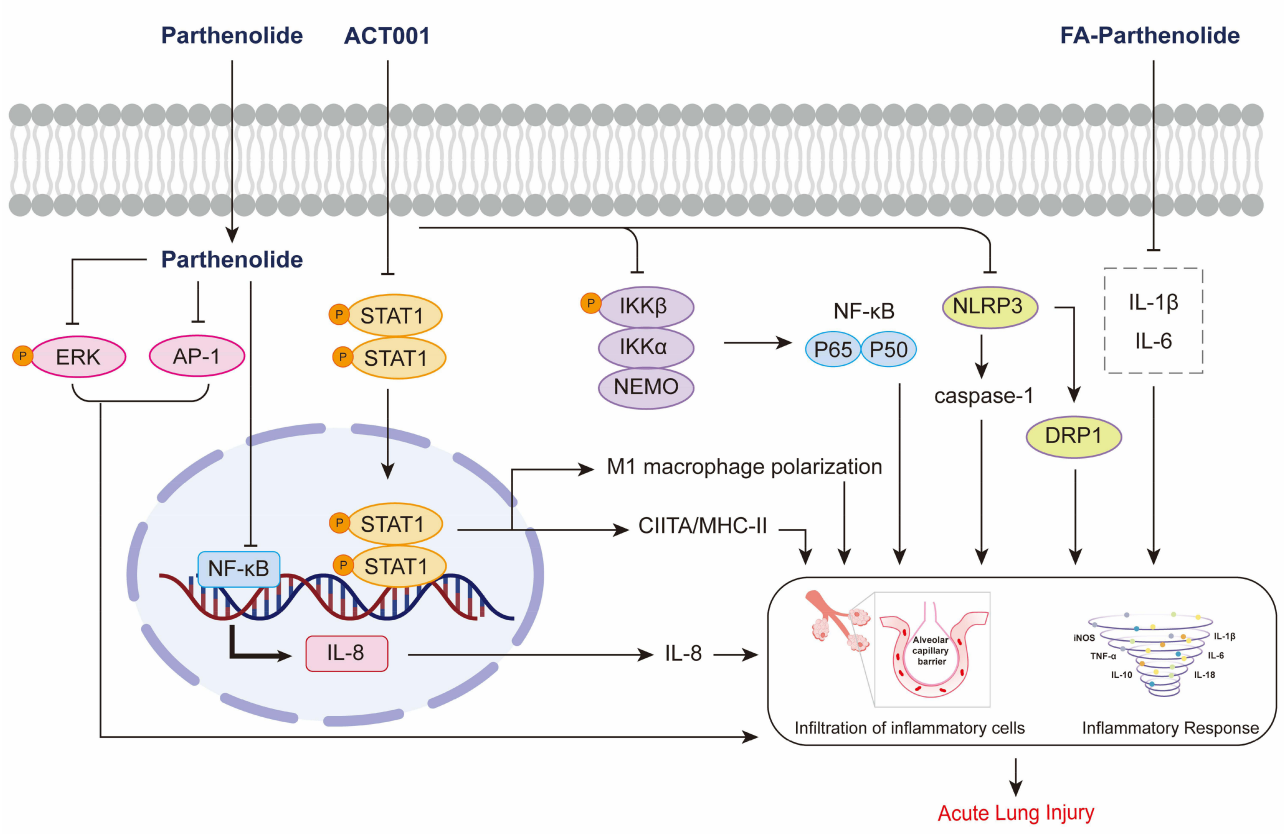

Figure 6 Molecular mechanisms of PTN and its derivatives in acute lung injury. Parthenolide (PTN) inhibits NF-κB and MAPK/AP-1 signaling, reducing IL-8 production and inflammatory cell infiltration. FA-PTN mitigates inflammation in ALI models. ACT001 exerts protective effects by: (i) inhibiting M1 macrophage polarization via suppression of p-IKKβ and p-STAT1; (ii) attenuating NLRP3/caspase-1-dependent pyroptosis through DRP1 regulation; and (iii) modulating AMPK/NF-κB pathways to reduce inflammation and pyroptosis. Collectively, these compounds preserve alveolar-capillary barrier integrity and attenuate ALI progression.

and predicts adverse clinical outcomes and mortality in these patients. As an anti-inflammatory agent, PTN can significantly reduce the production of IL-1, IL-2, IL-6, IL-8, and TNF-α in several human cell line models. In silico analysis identifies parthenolide as the most promising antiviral phytoconstituent from feverfew against SARS-CoV-2 PLpro and Mpro through molecular docking and dynamics simulations.[98] The obligate intracellular human pathogen *Chlamydia pneumoniae* is a widely distributed agent of usually mild infections of the respiratory tract.[99] Parthenolide induced Apoptosis in Mono Mac 6 cells by suppress NF-κB nuclear translocation.[80] Therefore, parthenolide may become one of the candidates for the clinical treatment of COVID-19.[100]

The Clinical Translation of Parthenolide and Its Derivatives in Respiratory Tract Diseases

Despite the well-documented preclinical efficacy of PTN and its derivatives in respiratory tract diseases, their clinical translation is still hampered by several critical bottlenecks. The primary bottleneck restricting the clinical use of natural PTN is its low aqueous solubility, with a reported maximum solubility of 0.169 μM in serum.[35] It is also accompanied by poor metabolic stability, short in vivo half-life, and insufficient tissue targeting.[3,101,102] At present, solutions to the above limitations are mainly divided into two categories: derivative optimization based on structural modification, and the development of novel drug delivery systems.

The Drug Delivery Systems of Parthenolide and Its Derivatives in Respiratory Tract Diseases

Structural modification of the PTN parent nucleus is the most straightforward strategy to optimize its solubility and pharmacokinetic properties. The representative derivatives DMAPT and ACT001 have made critical progress. DMAPT has 100–1000-fold higher aqueous solubility than natural PTN with up to 70% oral bioavailability and has completed a phase I clinical trial for relapsed/refractory hematological malignancies.[7] ACT001 exhibits superior plasma stability to DMAPT, with a prolonged half-life and reduced systemic toxicity, and this oral formulation with favorable bioavailability and safety has entered phase II clinical trials for interstitial lung diseases.[62] Other PTN derivatives, such as FA-PTN and C-14-modified PTN analogs, have also been reported to markedly improve aqueous solubility and exert enhanced anti-inflammatory or anti-tumor effects in respiratory disease models.[36,37]

The construction of targeted drug delivery systems is a key direction to overcome the limitations of PTN in clinical application. Preclinical studies have explored a variety of delivery platforms suitable for PTN in respiratory diseases. Gill et al developed a mixed micelle delivery system based on 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000 (PEG2000-DSPE) and vitamin E-D-alpha-tocopheryl polyethylene-glycol succinate (TPGS), which successfully achieved the co-delivery of paclitaxel and parthenolide, and significantly enhanced the cytotoxic effect on paclitaxel-sensitive and paclitaxel-resistant non-small cell lung cancer cell lines.[103] Xin Jin et al constructed a tLyp-1-modified long-circulating liposome co-delivery system to realize lung cancer-targeted delivery of parthenolide and ginsenoside compound K (CK), and confirmed that the combination of the two drugs exerts a synergistic anti-lung cancer effect and has favorable biosafety both in vitro and in vivo.[102] Dicarboxylic anhydride-crosslinked cyclodextrin nanosponges have been developed for the oral delivery of encapsulated parthenolide. This system can in situ transform into a hydrogel upon hydration in the colonic region, which combines the physical barrier protection of the ulcer surface and sustained drug release, thereby improving the aqueous solubility and chemical stability of parthenolide, and ultimately significantly alleviating ulcerative colitis in rat models.[104]

With the development of materials technology, liposomes, and micelles play an important role in drug delivery to lung cancer cells. Epidermal growth factor (EGF) -conjugated mixed micelles of PEG2000-DSPE and vitamin E-TPGS loaded with paclitaxel and PTN could reduce cancer cell viability.[60,103] PTN combined with ginsenoside compound K (CK) loading in tLyp-1-decorated liposomes, defined as CK/PTN tLyp-1 Liposomes, was shown to improve cancer treatment. The apoptosis rate, ROS levels and migration inhibition ratio of A549 cells in the CK/

PTN tLyp-1 Liposomes treatment group were almost 5-fold higher than those of the PTN single treatment group. In addition, the tumor growth of the CK/PTN tLyp-1 Liposomes treatment group was lower than that of the PTN single treatment group.[102] Xin Jin et al used a cocktail liposome loaded with PTN, betulinic acid, honoliol, and ginsenoside Rh2 to improve the efficacy of treatment and reduce the side effect.[58]

Although PTN and its derivatives exhibit a favorable safety profile in preclinical studies and clinical trials, standardized management of potential adverse reactions remains a key point to be standardized in clinical application. PTN has strong contact sensitization potential, and susceptible individuals may develop allergic contact dermatitis, oral mucosal ulceration, and even systemic allergic reactions, with a particularly high risk in those allergic to Asteraceae (Compositae) plants.[61,105] For clinical management, detailed allergy history inquiry should be conducted before administration. Once allergic reactions occur, the drug should be discontinued immediately, and anti-allergic treatment should be given as appropriate. In addition, the antiplatelet activity of PTN may increase the bleeding risk in patients receiving concurrent anticoagulant or antiplatelet drugs, and its use is not recommended in patients undergoing surgery.[106] It is recommended to discontinue PTN at least 2 weeks before elective surgery. Common gastrointestinal adverse reactions include abdominal pain, nausea, vomiting, diarrhea, dyspepsia, and flatulence.[12]

The Clinical Trials and Patents of Parthenolide and Its Derivatives in Respiratory Tract Diseases

Alongside structural optimization, researchers have extensively explored the clinical translation of parthenolide and its derivatives. In a completed phase II study, 44 adults with fibrotic lung disease received oral ACT001 at a daily dose of 400 mg. The treatment was well tolerated, slowed the decline of forced vital capacity, and achieved disease stabilization in approximately 50% of patients.[107] A Phase III clinical trial of ACT001 is currently underway, enrolling 270 patients with brain metastases from small cell lung cancer to compare and evaluate the efficacy and safety of ACT001 combined with whole-brain radiotherapy versus placebo plus the same radiotherapy regimen.[108] The clinical trials are outlined in the Table 3. Additionally, parthenolide and its derivatives have been granted multiple patents in the field of respiratory tract diseases, including lung cancer and leukotriene-mediated inflammatory diseases of the lungs. These patents cover diverse structural modifications, preparation methods, and pharmaceutical applications. Patents related to the clinical application of parthenolide are presented in Table 4.

Conclusion

At present, PTN and its derivatives have been studied worldwide in various respiratory tract diseases, including lung cancer, asthma, PF, PH, ALI and infectious lung diseases for their predominant pharmacological activity. Here, we have

Table 3 Clinical Trials of Parthenolide and Its Derivatives in Respiratory Tract Diseases

Stage	Compound	Study Population	Study Phase	Formulation and Administration Regimen	Outcomes	Reference
Completed	ACT001	44 adults (35 IPF, 9 fILD)	Phase II multicentre parallel-group study	100mg immediate-release capsule; 400mg oral daily for up to 52 weeks	Well-tolerated; slowed FVC decline, with disease stabilization in ~50% of patients.	[107]
Ongoing	ACT001	270 adults with SCLC brain metastases eligible for WBRT	Phase III randomized, blinded, placebo-controlled trial	400mg oral BID + WBRT; placebo + WBRT	Study ongoing; no results available	[108]

Table 4 Patent Overview of Parthenolide and Its Derivatives in the Field of Respiratory Tract Diseases

Title	Compound	Disease
Fluorine-containing parthenolide derivative, preparation method therefor and use Thereof	Fluorine-containing parthenolide derivatives of formula (I) and their pharmaceutically acceptable forms.	Lung cancer
Parthenolide derivatives and use thereof	Natural product-like compounds derived from parthenolide via chemoenzymatic scaffold editing/rearrangement of 9(S)-hydroxy-, 1,10-epoxy- or 14-hydroxy-parthenolide.	Lung cancer
Parthenolide-benzenesulfonylfuroxan derivatives and salts thereof, preparation methods and applications	Parthenolide-benzenesulfonylfuroxan derivatives; and their pharmaceutically acceptable forms.	Lung cancer
Parthenolide derivatives, methods for their preparation and their use as anticancer agents	Parthenolide derivatives functionalized at C9 and/or C14 via P450-catalyzed hydroxylation (including C9-substituted, C14-substituted, and 9,13-disubstituted derivatives)	Leukotriene-mediated inflammatorydiseases of lungs
Parthenolide derivatives and their modulation of processes controlled by regulated translation	Parthenolide derivatives that modulate processes controlled by regulated mRNA translation and exhibit anticancer activity.	Lung cancer
Deuterated dimethyl amine parthenolide, preparation method and use thereof in drug preparation	Deuterated dimethyl amine parthenolide	Lung cancer

summarized the effects and mechanisms of PTN and its derivatives as shown in Figure 7. Collectively, these findings suggest that PTN and its derivatives may be a potential drug for the treatment of respiratory diseases in the future.

Parthenolide, a sesquiterpene lactone derived from feverfew (*Tanacetum parthenium*), and its synthetic derivatives—most notably DMAPT and ACT001—have emerged as promising multifunctional agents for the treatment of respiratory tract diseases. This review comprehensively summarizes the therapeutic effects and underlying mechanisms of parthenolide and its derivatives across a broad spectrum of respiratory conditions, including lung cancer, asthma, pulmonary fibrosis, pulmonary hypertension, acute lung injury, tuberculosis, and pneumonia.

Accumulating evidence demonstrates that parthenolide and its derivatives exert their pharmacological effects through multiple signaling pathways, including NF-κB, STAT3, MAPK/ERK, PI3K/AKT, and p53, thereby modulating inflammation, oxidative stress, apoptosis, and immune responses. In lung cancer, these compounds inhibit tumor proliferation, metastasis, and chemoresistance while enhancing anti-tumor immunity. In non-neoplastic respiratory diseases such as pulmonary fibrosis and acute lung injury, they attenuate inflammation, reduce extracellular matrix deposition, and protect against tissue damage.

Despite these promising preclinical findings, the clinical translation of parthenolide has been historically limited by poor aqueous solubility, metabolic instability, and suboptimal bioavailability. To overcome these challenges, two complementary strategies have been developed: structural modification to generate more soluble derivatives (eg, DMAPT and ACT001), and the design of advanced drug delivery systems including liposomes, micelles, and nanoparticles. Notably, ACT001 has advanced to phase II/III clinical trials for lung cancer and radiation-induced lung injury, demonstrating favorable safety profiles and preliminary efficacy.

In conclusion, parthenolide and its derivatives represent a versatile class of natural product-based therapeutics with significant potential in respiratory medicine. By integrating mechanistic insights with advances in medicinal chemistry and targeted drug delivery, future research should focus on optimizing formulation strategies, establishing robust safety profiles, and conducting well-designed clinical trials to fully realize the therapeutic potential of these compounds for patients with respiratory diseases.

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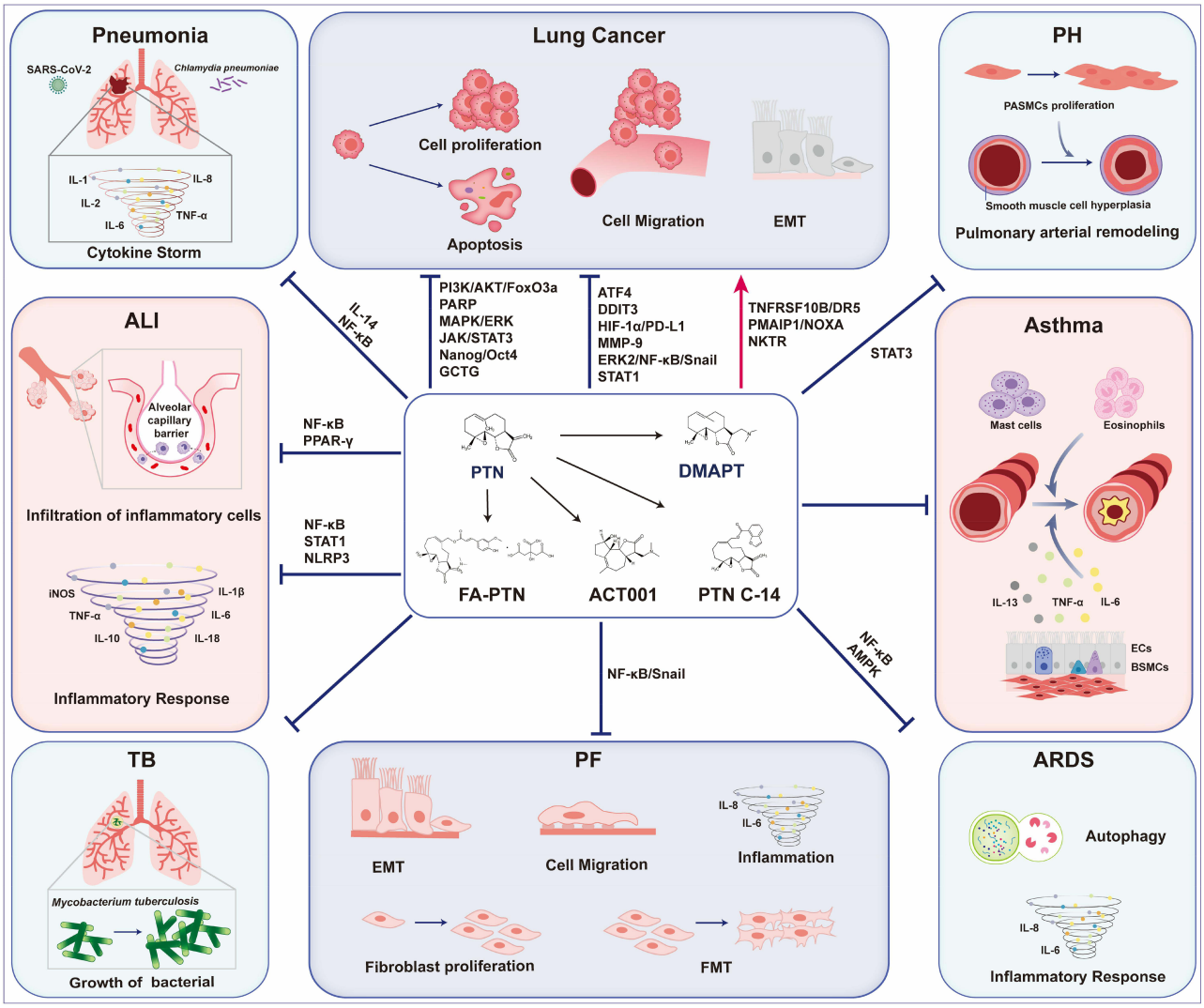

Figure 7 Schematic summary of the therapeutic mechanisms of PTN and its derivatives in respiratory diseases. Parthenolide (PTN) and its derivatives (DMAPT, ACT001, FA-PTN, PTN C-14) exert therapeutic effects across various respiratory pathologies through multiple mechanisms. In lung cancer, these compounds inhibit proliferation, migration, and EMT while inducing apoptosis via PI3K/AKT/FoxO3a, MAPK/ERK, JAK/STAT3, HIF-1α/PD-L1, and ERK2/NF-κB/Snail pathways, targeting GCTG, ATF4/DDIT3. In pulmonary hypertension (PH), PTN attenuates pulmonary arterial remodeling by inhibiting PASMC proliferation via STAT3 signaling. For asthma, PTN suppresses inflammatory cell infiltration and pro-inflammatory cytokines (IL-13, TNF-α, IL-6). In acute lung injury (ALI)/ARDS, PTN and derivatives attenuate inflammation, autophagy, and neutrophil infiltration by regulating NF-κB and AMPK pathways. In pulmonary fibrosis (PF), these compounds inhibit EMT, FMT, fibroblast proliferation, and inflammation through NF-κB/Snail pathway. Against pneumonia/tuberculosis, they inhibit bacterial growth and suppress SARS-CoV-2-induced cytokine storms (IL-1, IL-2, IL-6, TNF-α).

Abbreviations

AEC, alveolar epithelial cells; AHR, airway hyperresponsiveness; AKT, AKT serine/threonine kinase; ALI, acute lung injury; AMPK, AMP-activated protein kinase; AP-1, activator protein 1; ARDS, acute respiratory distress syndrome; ATF4, activating transcription factor 4; αMγB, α-exo-methylene-γ-butyrolactone; α-SMA, alpha-smooth muscle actin; Bax, BCL2 associated X, apoptosis regulator; Bcl-2, B-cell lymphoma 2; BEAS-2B, bronchial epithelial cell line 2B; BRCA1, breast cancer 1; BSM, bronchial smooth muscle; caspase-3, cysteinyl aspartate specific proteinase 3; c-FLIP, CASP8 and FADD-like apoptosis regulator; CF, cystic fibrosis; CFLAR, CASP8 and FADD-like apoptosis regulator; CK, compound K; CLP, cecal ligation and puncture; COVID-19, coronavirus disease 2019; Cyclin D1, cyclin D1; DDIT3, DNA damage inducible transcript 3; DMAMCL, dimethylaminomicheliolide; DMAPT, dimethylamino parthenolide; DMSO, dimethyl sulfoxide; DR5, death receptor 5; DRP1, dynamin related protein 1; DSB, double-strand break; eIF4E, eukaryotic translation initiation factor 4E; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EIF2A, eukaryotic translation initiation factor 2 subunit alpha; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-regulated

kinase; ERN1, endoplasmic reticulum to nucleus signaling 1; FA, ferulic acid; FANCD2, FA complementation group D2; FA-PTN, ferulic acid-parthenolide; FMT, fibroblast-to-myofibroblast transition; FoxO3α, forkhead box O3α; GCTG, γ-glutamyltransferase; GGCT, gamma-glutamylcyclotransferase; GSH, glutathione; HAC, human adenocarcinoma cell lines; HIF-1α, hypoxia inducible factor 1 subunit alpha; HR, homologous recombination; HSPA5, heat shock protein family A member 5; HSCC, human squamous cell carcinoma cell lines; IC_{50}, half maximal inhibitory concentration; ICIs, immune checkpoint inhibitors; IGF-1R, insulin-like growth factor 1 receptor; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IPF, idiopathic pulmonary fibrosis; JAK2, Janus kinase 2; JNK, Jun N-terminal kinase; LUAD, lung adenocarcinoma; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; Mcl-1, myeloid cell leukemia 1; MEK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; MMP-9, matrix metalloproteinase 9; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHEJ, non-homologous end joining; NKTR, natural killer triggering receptor; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; NSCLC, non-small-cell lung cancer; Olig2, oligodendrocyte lineage transcription factor 2; OS, overall survival; PARP, poly ADP-ribose polymerase; PASMCs, pulmonary artery smooth muscle cells; p70S6K, ribosomal protein S6 kinase B1; PF, pulmonary fibrosis; PH, pulmonary hypertension; PI3K, phosphoinositide 3-kinase; PMAIP1, phorbol-12-myristate-13-acetate-induced protein 1; PPAR-γ, peroxisome proliferator-activated receptor gamma; PTN, parthenolide; RAD51, RAD51 recombinase; RAF, rapidly accelerated fibrosarcoma; RILI, radiation-induced lung injury; ROS, reactive oxygen species; RV, right ventricular; SAHA, suberoylanilide hydroxamic acid; SCLC, small-cell lung cancer; SOD, superoxide dismutase; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducers and activators of transcription 3; TB, tuberculosis; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; TNFRSF10B, tumor necrosis factor receptor superfamily member 10B (death receptor 5, DR5); TPGS, D-alpha tocopheryl polyethyleneglycol succinate; VEGF, vascular endothelial growth factor; 4EBP1, eukaryotic translation initiation factor 4E binding protein 1.

Data Sharing Statement

All data are available from the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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