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REVIEW

The Prospects of Palmitylethanolamide in Tumor Prevention and Treatment

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Abstract: Palmitoylethanolamide (PEA) is an endogenous fatty acid amide that has garnered significant attention due to its potential multiple antitumor mechanisms. This review first explores the current statuses and challenges faced in tumor prevention and treatment, pointing out the toxic side effects of traditional chemotherapy and radiotherapy as well as the issue of drug resistance in tumor cells, particularly adverse reactions such as decreased immune function caused by chemotherapy and radiotherapy. It further analyzes the relationship between inflammation, immune evasion in the tumor microenvironment, and tumor growth and metastasis. Subsequently, it discusses multi-target therapy strategies, introducing PEA as an emerging therapeutic candidate whose anti-inflammatory, pro-apoptotic, anti-angiogenic, and antioxidant effects show great promise in tumor prevention and treatment. Preclinical research and preliminary clinical trial results indicate its safety and efficacy, supporting its role as an adjunct in tumor treatment. In addition, innovative explorations that combine modern drug delivery systems with combination therapy strategies are proposed, aiming to enhance the bioavailability and therapeutic effectiveness of PEA. Finally, the future of personalized precision treatment and combination therapy models is anticipated to bring new hope for tumor prevention and treatment.

Keywords: tumor prevention and treatment, palmitylethanolamide, multi-target therapy, anti-tumor mechanisms, clinical application

Introduction

Current Situation and Challenges in Tumor Prevention and Treatment

Tumors, as a serious disease that poses a significant threat to human health, have high incidence and mortality rates that have become a severe challenge faced by global public health.[1–3] Every year, millions of people worldwide are diagnosed with various types of cancer, and a considerable number of patients ultimately lose their lives due to tumors.[4] Therefore, how to effectively prevent and treat tumors has become an important topic in medical research (Figure 1).

Toxic Side Effects of Chemotherapy and Radiotherapy and Issues of Drug Resistance

Chemotherapy and radiotherapy are commonly used methods for treating tumors in clinical practice, aimed at achieving therapeutic effects by killing or inhibiting the growth of cancer cells. However, these treatment methods also have toxic side effects on normal cells, leading to a series of adverse reactions, such as nausea, vomiting, hair loss, and decreased immune function.[5–7] More importantly, tumor cells are prone to developing resistance under long-term chemotherapy or radiotherapy, which gradually reduces the effectiveness of treatment and ultimately leads to treatment failure. The mechanisms of tumor cell resistance are complex and varied, including changes in the expression of drug transport proteins.[8]

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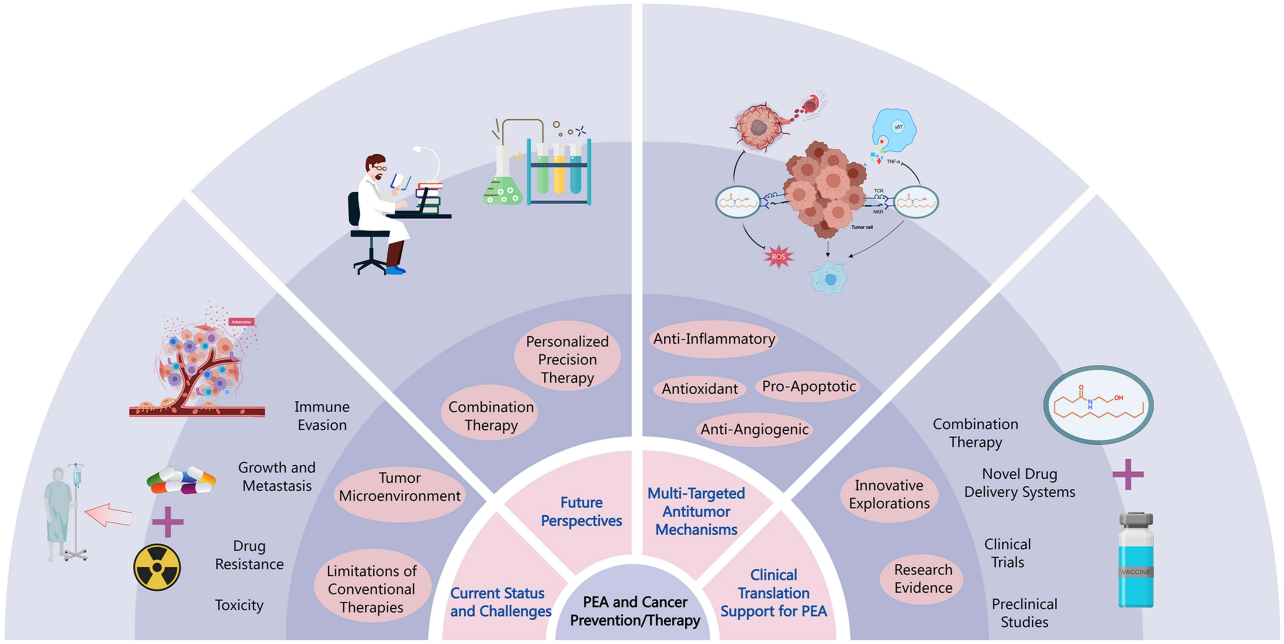
Graphical Abstract



Inflammation and Immune Evasion Mechanisms in Tumor Microenvironment

Tumor microenvironment refers to the local environment where tumor cells reside, composed of tumor cells, stromal cells, immune cells, blood vessels, as well as various cytokines and growth factors. The tumor microenvironment has a significant impact on tumor growth, metastasis, and drug resistance.[9–11] Inflammation plays a dual role in the occurrence and development of tumors;[12–15] on one hand, the inflammatory response can activate the immune system to kill tumor cells; on the other hand, chronic inflammation can promote the proliferation, angiogenesis, and metastasis of tumor cells. Moreover, tumor cells can evade surveillance and attack by the immune system through various mechanisms, such as inhibiting the activity of immune cells and inducing immune tolerance.[16–18]

The Importance of Multi-Target Treatment Strategies

Traditional cancer treatments often target a single point, which can easily lead to drug resistance or metastasis in tumor cells. Therefore, multi-target strategies are receiving increasing attention. Multi-target treatment refers to interventions that simultaneously target multiple biomarkers and signaling pathways of tumor cells, thereby more effectively suppressing tumor growth and metastasis. Compared to single-target treatments, multi-target treatments have the following advantages: they can simultaneously inhibit multiple growth signals of tumor cells, reduce the occurrence of drug resistance; they can modulate the tumor microenvironment, enhancing the immune system's anti-tumor effects; and they can improve treatment efficacy and prolong patient survival.[19,20]

Addressing the Needs of Inflammation, Angiogenesis, and Cell Apoptosis

The occurrence and development of tumors is a complex process that involves multiple links, including inflammation, angiogenesis, and apoptosis.[21,22] Therefore, multi-target therapy needs to intervene in these links simultaneously. For example, anti-inflammatory drugs can be used to suppress the inflammatory response in the tumor microenvironment;[23,24] anti-angiogenic drugs can be used to inhibit the tumor's angiogenesis, cutting off the tumor's nutrient supply; and pro-apoptotic drugs can be used to induce tumor cell apoptosis.[25–27]

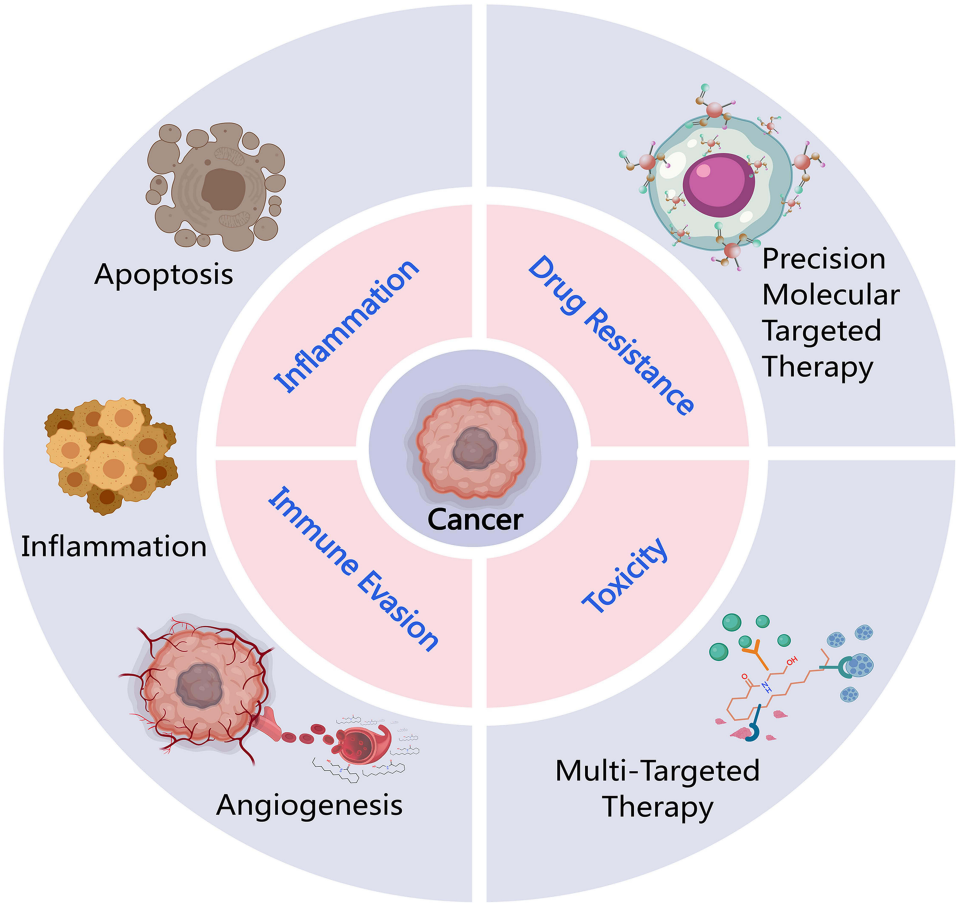


Figure 1 Bottlenecks in tumor treatment and the potential side effects as well as future treatment strategies.

New Trends in Molecular Precision Therapy and Translational Medicine

Molecular precision therapy is an emerging direction in the field of tumor treatment in recent years. It detects the genes, proteins, and other molecules of tumor cells to identify the driving genes and key signaling pathways of tumors, and then it uses drugs targeting these sites for treatment. Molecular precision therapy can enhance the targeting and effectiveness of treatment, reducing damage to normal cells. Translational medicine serves as a bridge that rapidly transforms the results of basic research into clinical applications. Through translational medicine, new molecular targets and treatment methods can be quickly applied in clinical settings, improving the level of tumor treatment.[28–30] The combination of molecular precision therapy and translational medicine will bring new hope for personalized treatment of tumors.

Biological Characteristics of PEA and Its Potential Values in Tumor

The Structure and Synthesis Pathways of Endogenous Fatty Acid Amides

PEA is a bioactive lipid mediator, a member of the N-acyl-ethanolamine (NAE) fatty acid amide family. It was isolated for the first time from soybeans, egg yolk and peanut meal. The biosynthesis of PEA is “on demand” within the lipid bilayer. The enzyme N-acyl-phosphatidyl-ethanolamine-selective phospholipase D (NAPE-PLD) generates PEA in animals by hydrolyzing its direct phospholipid precursor, N-palmitoyl-phosphatidyl-ethanolamine. Fatty acid amide hydrolase (FAAH) and N-acylethanolamine-hydrolyzing acid amidase (NAAA) can degrade PEA into palmitic acid and ethanolamine.[31] PEA has various biological activities, including anti-inflammatory, analgesic, and neuroprotective effects. In recent years, studies have found that PEA also has potential applications in tumor prevention and treatment (Figure 2).[32]

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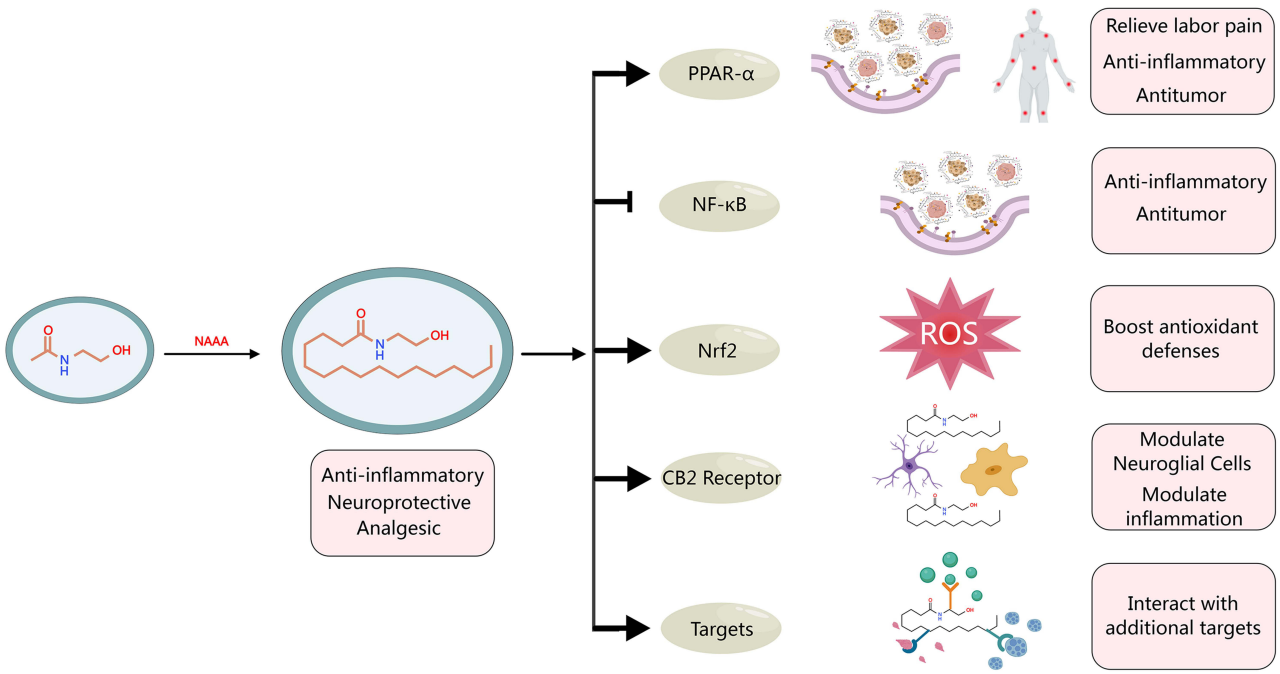

Figure 2 Sources of PEA, synthesis pathways, nutritional effects, and potential action targets.

Main Action Targets

The biological effects of PEA are mainly achieved by activating or regulating multiple targets, which include:

PPAR-α (Peroxisome Proliferator-Activated Receptor Alpha): PPAR-α is a nuclear receptor involved in processes such as fatty acid metabolism, inflammation, and cell proliferation. PEA can exert anti-inflammatory, analgesic, and antitumor effects by activating PPAR-α.[33,34]

NF-κB (nuclear factor kappa B): NF-κB is an important transcription factor that is involved in processes such as inflammation, immunity, and apoptosis. PEA can exert anti-inflammatory and anti-tumor effects by inhibiting the activity of NF-κB.[35–37]

Nrf2 (nuclear factor erythroid 2-related factor 2): Nrf2 is a transcription factor that plays a role in the cellular antioxidant defense. PEA can enhance the antioxidant capacity of cells and protect them from oxidative damage by activating Nrf2.[36,38]

CB2 (Cannabinoid type 2) receptor: PEA can regulate neuroinflammation by activating the CB2 receptor and affecting glial cells.[39,40]

Other targets: PEA may also exert effects through other targets, such as GPR55 (G protein coupled receptor 55).[41]

Overview of Objectives and Overall Framework

This review aims to comprehensively elucidate the mechanisms of action and clinical evaluation of PEA in tumor prevention and treatment. By summarizing and analyzing existing studies, it explores the roles of PEA in anti-inflammation, anti-angiogenesis, pro-apoptosis, and antioxidant effects, as well as its application effects in different tumor models. At the same time, it assesses the clinical trial data and safety of PEA, and it looks forward to the application prospects of PEA in tumor prevention and treatment.

To better understand the role of PEA in tumor prevention and treatment, this review will be organized according to the following framework: first, to introduce the current status and challenges of tumor prevention and treatment, as well as the importance of multi-target therapy strategies; second, to delve into the anti-tumor mechanisms of PEA, including anti-inflammation and immune regulation, anti-angiogenesis, pro-apoptosis and anti-proliferation mechanisms, as well as antioxidant and DNA protective effects; then, to summarize the clinical evaluation of PEA, including preclinical studies

and in vitro experiments, as well as clinical trial data and patient safety analyses; next, to present PEA delivery systems and combination therapy strategies, including novel drug delivery systems and combination therapy strategies; finally, to address the current challenges in research and future directions, including in-depth discussions of molecular mechanisms and signaling pathways, clinical trial design and optimization, as well as improvements in novel delivery systems and combination medication regimens. Through this framework, we strive to comprehensively and systematically articulate the role of PEA in tumor prevention and treatment, providing a reference for future research and applications.

The Anti-Tumor Mechanism of PEA (Figure 3)

Anti-Inflammation and Immunoregulation

Inhibition of Pro-Inflammatory Signaling Pathways (Figure 3A)

Chronic inflammation in the tumor microenvironment is an important factor in tumor occurrence, development, and metastasis.[42–44] NF-κB and COX-2 are key signaling molecules in the inflammatory response that regulate the expression of various pro-inflammatory genes, thereby promoting tumor growth and metastasis.[45–47] PEA can effectively alleviate the inflammatory response in the tumor microenvironment by inhibiting these pro-inflammatory signaling pathways.[35–37]

PEA inhibits the NF-κB signaling pathway through various mechanisms. NF-κB typically exists in the cytoplasm in a form bound to the inhibitor protein IκB. When stimulated by inflammation, IκB is phosphorylated and degraded, releasing NF-κB into the nucleus to activate the transcription of downstream genes. PEA can inhibit the phosphorylation

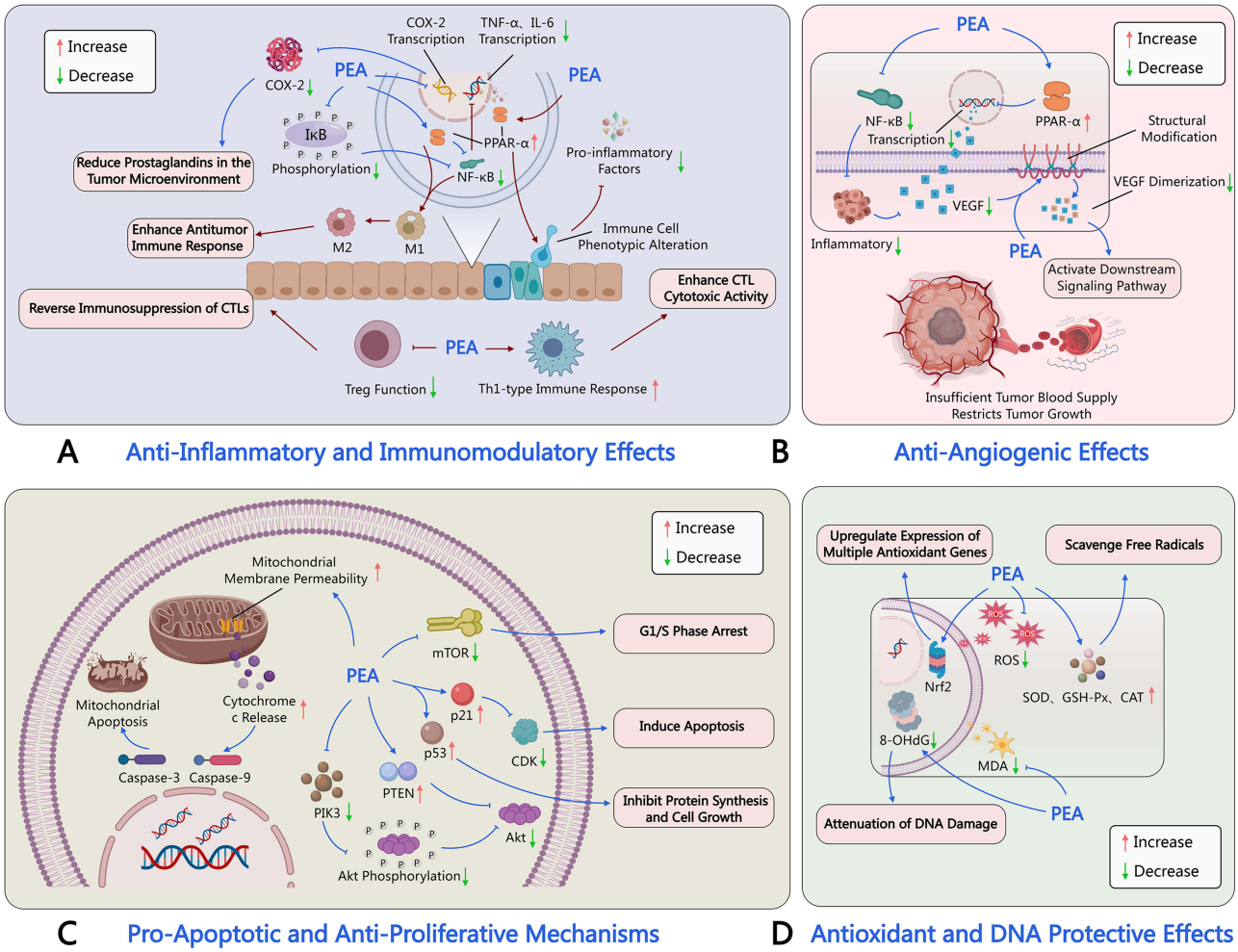

Figure 3 Antitumor mechanisms of PEA. (**A**) Anti-inflammatory and immune-regulatory effects of PEA; (**B**) Anti-angiogenic effects of PEA; (**C**) Pro-apoptotic and anti-proliferative mechanisms of PEA; (**D**) Antioxidant and DNA protective effects mediated by PEA.

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and degradation of IκB, thereby preventing the activation of NF-κB. Additionally, PEA can indirectly inhibit NF-κB activity by activating PPAR-α. The activation of PPAR-α can interfere with the DNA binding capability of NF-κB, thus suppressing its transcriptional activity.[48,49]

COX-2 is a key enzyme in the arachidonic acid metabolic pathway, responsible for synthesizing pro-inflammatory mediators such as prostaglandins. In many tumor cells, COX-2 expression is significantly upregulated, leading to elevated levels of prostaglandins in the tumor microenvironment, which in turn promotes tumor angiogenesis, immune evasion, and metastasis. PEA can inhibit the expression of COX-2, thereby reducing the levels of prostaglandins in the tumor microenvironment. Its mechanisms may include direct inhibition of COX-2 gene transcription or indirect inhibition mediated by PPAR-α.[50,51]

The inhibitory effect of PEA on the NF-κB and COX-2 signaling pathways has significant clinical implications. By reducing tumor-associated inflammation, PEA can inhibit tumor growth and metastasis, improving patient prognosis. Moreover, the inhibition of NF-κB and COX-2 also helps to enhance the sensitivity of tumor cells to chemotherapy and radiotherapy, thereby improving treatment outcomes.

Regulation of the Production of Cytokines and Polarization of Immune Cells (Figure 3A)

The cytokine network in the tumor microenvironment is complex, with pro-inflammatory cytokines such as TNF-α and IL-6 playing a key role in tumor occurrence and development. TNF-α can promote the proliferation, angiogenesis, and metastasis of tumor cells, while inhibiting anti-tumor immune responses. IL-6 can promote the survival and resistance of tumor cells, and it is involved in tumor-associated inflammatory responses. PEA can regulate the production of these pro-inflammatory cytokines, thereby exerting anti-tumor effects.

PEA can regulate the production of TNF-α and IL-6 through multiple mechanisms. First, PEA can inhibit the NF-κB signaling pathway, thereby reducing the transcription of TNF-α and IL-6 genes. Secondly, PEA can also inhibit the release of pro-inflammatory cytokines by activating PPAR-α. The activation of PPAR-α can alter the phenotype of immune cells, for example, promoting macrophage polarization to the M2 type, thereby reducing the production of pro-inflammatory cytokines.[52–54]

Immune cells play a dual role in the tumor microenvironment. On one hand, some immune cells (such as cytotoxic T cells and natural killer cells) can directly kill tumor cells, exerting anti-tumor immune responses. On the other hand, other immune cells (such as tumor-associated macrophages and myeloid-derived suppressor cells) can promote tumor growth and metastasis, leading to immune evasion. PEA can enhance anti-tumor immune responses by regulating the functions of immune cells.

Macrophages are one of the most abundant immune cells in the tumor microenvironment. Based on their functional characteristics, macrophages can be divided into M1 and M2 types. M1 macrophages primarily produce pro-inflammatory cytokines to kill tumor cells. In contrast, M2 macrophages mainly produce anti-inflammatory cytokines, promoting tumor angiogenesis and immune evasion. PEA can promote the polarization of macrophages towards the M1 type, thereby enhancing the anti-tumor immune response. Its mechanisms may include the activation of PPAR-α, inhibition of NF-κB, and regulation of cytokine signaling pathways.[55,56]

T cells are another important type of immune cell that play a key role in tumor immunity. Cytotoxic T cells (CTLs) can recognize and kill tumor cells, while helper T cells (Th cells) can regulate the activity of CTLs. PEA can promote Th1-type immune responses, enhancing the killing ability of CTLs. In addition, PEA can also inhibit the function of regulatory T cells (Tregs), thereby release the immune suppression on CTLs.[57]

In summary, PEA can effectively regulate the immune response in the tumor microenvironment by modulating the production of cytokines and the polarization of immune cells, thereby exerting antitumor effects.

Anti-Angiogenic Effects

Inhibition of the VEGF Signaling Pathway and Neovascularization (Figure 3B)

Angiogenesis, the formation of new blood vessels, is a key step in tumor growth, invasion, and metastasis.[58–60] Tumors require an ample blood supply to sustain their rapid growth and metabolic needs. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are the main regulatory factors in the angiogenesis process. VEGF promotes the

generation of new blood vessels by binding to VEGFR, activating downstream signaling pathways that enhance the proliferation, migration, and lumen formation of endothelial cells. PEA can inhibit tumor angiogenesis by blocking the VEGF signaling pathway, thereby suppressing tumor growth and metastasis.[61]

PEA can inhibit the VEGF signaling pathway through various mechanisms. First, PEA can reduce the expression level of VEGF. The expression of VEGF in tumor cells and other cells in the tumor microenvironment (such as macrophages) is regulated by various factors, including hypoxia, inflammation, and growth factors. PEA can indirectly inhibit the expression of VEGF by suppressing the NF-κB signaling pathway, thus reducing the inflammatory response. Furthermore, PEA can also directly inhibit the transcription of the VEGF gene by activating PPAR-α.[62,63]

Secondly, PEA can inhibit the activation of VEGFR. After VEGF binds to VEGFR, it causes the dimerization and phosphorylation of VEGFR, activating downstream signaling pathways such as the PI3K/Akt and MAPK pathways. PEA can block the activation of these downstream signaling pathways by inhibiting the phosphorylation of VEGFR. Its mechanism may involve direct binding to VEGFR or altering the lipid raft structure of the cell membrane, which affects the dimerization of VEGFR.[62,63]

Both the in vitro angiogenesis experiments and the analysis of vascular density in animal models showed that PEA significantly inhibits angiogenesis. In in vitro experiments, PEA can inhibit the proliferation, migration, and lumen formation of endothelial cells. In animal models, PEA can reduce the vascular density in tumor tissues, decreasing the blood supply to the tumor.[64]

Reduce Tumor Blood Supply and Restrict Tumor Growth (Figure 3B)

PEA can reduce the blood supply to tumors by inhibiting angiogenesis, thereby limiting tumor growth and metastasis. Tumor growth and metastasis require a large amount of energy and nutrients, which are primarily supplied through blood. By inhibiting angiogenesis, PEA can cut off the blood supply to tumors, leading to hypoxia and nutrient deficiency in tumor cells, thus suppressing tumor growth.[64]

The treatment of solid tumors usually requires a combination of various therapeutic methods, including surgery, radiotherapy, chemotherapy, and targeted therapy. The anti-angiogenic effect of PEA gives it potential value in the treatment of solid tumors. Especially when used in combination with other anti-angiogenic drugs, PEA may exert a synergistic effect, enhancing the therapeutic efficacy.

Mechanisms of Promoting Apoptosis and Antiproliferation

Upregulation of Pro-Apoptotic Genes and Cell Cycle Arrest (Figure 3C)

The apoptosis of tumor cells is regulated by multiple factors, including the expression levels of pro-apoptotic and anti-apoptotic genes. BAX is one of the members of the pro-apoptotic gene family Bcl-2, capable of promoting the permeability of the mitochondrial membrane, releasing cytochrome c, and activating the Caspases cascade, ultimately leading to cell apoptosis. Caspases are a class of proteolytic enzymes that play a key role in the process of apoptosis. PEA can promote the apoptosis of tumor cells by upregulating the expression of pro-apoptotic genes (such as BAX, Caspase-3/9).

The cell cycle is the foundation of cell proliferation, and abnormal expression of cell cycle regulatory proteins can lead to unlimited cell proliferation. Cell cycle arrest refers to the obstruction of the cell cycle process, preventing it from entering the next phase. PEA can inhibit tumor cell proliferation by inducing cell cycle arrest (such as G1/S phase arrest).[64]

The impact of PEA on mitochondrial apoptosis pathways and cell cycle regulatory proteins is as follows:

Mitochondrial apoptosis pathway: PEA can increase the permeability of the mitochondrial membrane, promote the release of cytochrome c, and activate Caspase-9 and Caspase-3, thereby initiating the mitochondrial apoptosis pathway.[64]

Cell cycle regulatory proteins: PEA can increase the expression of p21 and p53, where p21 inhibits the activity of cyclin-dependent kinases (CDKs), leading to G1/S phase arrest. p53, on the other hand, can activate DNA repair mechanisms or, when DNA damage cannot be repaired, induce apoptosis.

Cell experimental data indicate that PEA can significantly inhibit the proliferation of tumor cells and induce their apoptosis. PEA exhibits significant antitumor activity in various tumor cell lines.

Regulation of Akt/mTOR Signaling Mediated by PPAR-α (Figure 3C)

The Akt/mTOR signaling pathway is a key regulatory pathway for cell survival and proliferation. Akt is a serine/threonine protein kinase that can activate downstream mTOR, thereby promoting protein synthesis, cell growth, and proliferation. In many tumor cells, the Akt/mTOR signaling pathway is persistently activated, leading to abnormal proliferation and survival of tumor cells.

PPAR-α is a nuclear receptor that can regulate the expression of various genes, including those involved in lipid metabolism, inflammatory responses, and cell proliferation. PEA, as an agonist of PPAR-α, can inhibit the Akt/mTOR signaling pathway by activating PPAR-α, thereby suppressing the survival and proliferation of tumor cells.[63,65]

The interaction between PPAR-α and the Akt/mTOR pathway and its regulatory role in tumor cells is as follows:

Activation of PPAR-α can inhibit the activity of PI3K, which is the upstream kinase of Akt. The decrease in PI3K activity leads to a reduction in the phosphorylation level of Akt, thereby inhibiting the activity of Akt. Activation of PPAR-α can increase the expression of PTEN, which is a phosphatase that dephosphorylates Akt, thereby inhibiting Akt activity. Furthermore, activation of PPAR-α can inhibit the activity of mTOR, which is a downstream target of Akt, and the reduction of mTOR activity will lead to the suppression of protein synthesis and cell growth.

Relevant studies indicate that PEA can inhibit the Akt/mTOR signaling pathway by activating PPAR-α, thereby exerting anti-tumor effects.[62,63] In PPAR-α knockout cells, the anti-tumor activity of PEA is significantly reduced, suggesting that PPAR-α is an important target for the anti-tumor effects of PEA.

Antioxidant and DNA Protective Effects (Figure 3D)

Alleviation of Oxidative Stress and Improvement of Cellular Antioxidant Defense

Oxidative stress refers to a state of imbalance between the oxidation and antioxidant systems in the body, leading to the excessive production of oxidative substances. The level of oxidative stress in the tumor microenvironment is often high, primarily due to the vigorous metabolic activity of tumor cells and the infiltration of inflammatory cells in the tumor microenvironment. Oxidative stress can damage cellular DNA, proteins, and lipids, promoting the occurrence and development of tumors.[66–68]

The Nrf2 pathway is an important pathway for cellular antioxidant defense. Nrf2 is a transcription factor that can activate the expression of various antioxidant genes, including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT).[69,70] These antioxidant enzymes can eliminate free radicals in the body, protecting cells from oxidative damage. PEA can alleviate oxidative stress in the tumor microenvironment by activating the Nrf2 pathway or other antioxidant mechanisms.

The effects of PEA on oxidative stress markers and antioxidant enzymes are as follows:

Oxidative stress markers: PEA can reduce the levels of reactive oxygen species (ROS) and malondialdehyde (MDA); ROS is the main form of free radicals, and MDA is a product of lipid peroxidation. Elevated levels of these indicators signify an increase in oxidative stress.

Antioxidant enzymes: PEA can increase the activity of SOD, GSH-Px, and CAT, which are antioxidant enzymes that can eliminate free radicals in the body and protect cells from oxidative damage.[71]

The antioxidant effect of PEA has important clinical significance. By alleviating oxidative stress in the tumor microenvironment, PEA can protect normal cells from damage by tumor cells and improve patients' quality of life. In addition, PEA can also enhance the sensitivity of tumor cells to radiotherapy and chemotherapy, improving treatment efficacy.

Protecting Normal Cell DNA from Chemotherapy Damage

Chemotherapy is one of the important means of treating tumors, but chemotherapy drugs, while killing tumor cells, can also damage normal cells. DNA damage is one of the main toxic side effects of chemotherapy drugs. Chemotherapy drugs can directly or indirectly damage DNA, leading to DNA strand breaks, base modifications, and cross-linking. DNA damage can result in cell apoptosis, mutations, and carcinogenesis.

PEA can protect normal cells by reducing DNA damage or enhancing DNA repair mechanisms. PEA can decrease the levels of 8-hydroxydeoxyguanosine (8-OHdG), which is a marker of oxidative DNA damage, and a decrease in its levels

indicates reduced DNA damage. Furthermore, PEA can also enhance the activity of DNA repair enzymes, promoting the repair of DNA damage.[72]

In chemotherapy or radiotherapy models, PEA can significantly reduce DNA damage levels in normal cells, protecting them from the damage caused by chemotherapy or radiotherapy. This indicates that PEA has the potential to serve as an adjunctive agent in chemotherapy, reducing treatment side effects and improving patient tolerance.

Preclinical and Clinical Evaluation of PEA

Preclinical Research and in vitro Experiments

Antitumor Effect Data in Different Tumor Models

PEA exhibits potential anti-tumor activity in various tumor models. A study indicated that in the 7,12-dimethylbenz[a] anthracene (DMBA) induced breast tumor rat model, PEA treatment significantly reduced tumor area and volume, with the real-time monitoring of tumor progression slowdown through photoacoustic imaging.[64] Compared to the DMBA-induced tumor rat group, the PEA treatment group showed an increase in average oxygen saturation (sO2%) and a decrease in average total hemoglobin (HbT %), indicating that PEA can alleviate hypoxia-induced angiogenesis in tumors.[64] Histopathological examinations further confirmed that PEA mitigated DMBA-induced breast cancer, hepatotoxicity, and nephrotoxicity.[64]

In vitro studies also support the antitumor potential of PEA. In another study, PEA had a protective effect on endothelial cells, which is related to PEA's involvement in the angiogenesis process by affecting endothelial cell function. In glioblastoma U87MG cells, PEA significantly reduced the expression and secretion of hypoxia-induced VEGF mRNA, thereby inhibiting angiogenesis.

Discussion on the Effects of Proliferation, Apoptosis, and Angiogenesis in vitro

At the cellular level, PEA exhibits multiple regulatory effects on tumor cell proliferation, apoptosis, and angiogenesis (Table 1). A study found that PEA could inhibit the proliferation of MDA-MB-231 and MCF-7 breast cancer cells, alter nuclear morphology, and weaken the cell's wound healing ability. Molecular mechanism studies indicate that PEA induces apoptosis by upregulating the cell cycle arrest gene P21, tumor suppressor gene P53, pro-apoptotic genes Bax, Caspase-8, and FADD, while downregulating the anti-apoptotic gene BCL-2. In addition, PEA can upregulate the active form of Caspase-3, further confirming its pro-apoptotic capacity.

Table 1 The Application of PEA in Cancer-Related Preclinical Studies

Cancer Type	Main Receptors/ Targets	Results	Ref.
Colon cancer	PPAR-α GPR55	Um-PEA reduces tumor cell migration by inducing cell cycle arrest at G2/M phase and inhibits colon cancer cell proliferation by down-regulating MMP2 and TIMP1 expression.	[62,73]
Hepatocellular carcinoma	/	AEA and PEA levels are significantly elevated in HCC patients infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), serving as potential biomarkers for distinguishing HCC from liver cirrhosis infections.	[74]
Neuroblastoma	PPAR-α	OEA and PEA enhance IFNβ-mediated PD-L1 induction and p38 MAPK phosphorylation, promoting IFNβ-mediated apoptosis.	[75]
Glioma	PPAR-α	Culturing astrocytes with PEA can enhance the expression of P450scc, increase mitochondrial cholesterol availability, and subsequently convert it into progesterone, providing protective effects on neurons and glial cells.	[76]
Breast cancer	NF-κB FAAH TRPV1	PEA or AM11095 inhibited the secretion of IL-6 and IL-8, reduced the activation of NF-kB pathway, decreased the expression of VEGF and placental growth factor (PLGF) in TNBC, and suppressed tumor cell migration in vitro.	[77]
Endometrial cancer	GPR55	The decreased expression of FAAH, or the increased expression of NAPE-PLD, or both together may be the reason for the higher levels of PEA in endometrial cancer tissues.	[78]
Myeloproliferative neoplasms	CB2	At higher OEA/PEA ratios, MF patients may experience potential imbalance in NAE equilibrium.	[79]
Melanoma	/	The combined use of PEA and FAAH inhibitor URB597 promotes melanoma cell death and delays tumor growth in vivo.	[80]
Leukemia (RBL-2H3)	/	PEA is transported into RBL-2H3 cells through passive diffusion and facilitated transport.	[81]

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In neuroblastoma SH-SY5Y cells, the combined use of PEA and interferon β (IFNβ) can enhance IFNβ-induced apoptosis, manifested by increased cleavage of caspase 3 and poly-(ADP ribose) polymerase (PARP), as well as decreased levels of survivin and IκBα.[75] Meanwhile, PEA and OEA also increased the phosphorylation of p38/MAPK and the expression of programmed cell death ligand 1 (PD-L1) on the cell membrane surface.[75]

In addition, PEA also affects angiogenesis. In vitro experiments have shown that PEA can inhibit the inflammation-related VEGF signaling pathway, which is associated with the regulation of the Akt/mTOR pathway. Specifically, PEA reduces the release of VEGF and the formation of new blood vessels through a selective PPAR-αdependent mechanism, thereby inhibiting colitis-related angiogenesis.[63]

Analysis of Clinical Trial Data and Patient Safety

Preliminary Validation of the Anti-Tumor and Adjuvant Effects of PEA

Currently, clinical research data on PEA in tumor treatment is relatively limited, mainly focusing on case reports and small sample trials, primarily exploring its preliminary efficacy in chemotherapy induced side effects (Table 2). One study indicates that PEA shows potential in improving chemotherapy-induced peripheral neuropathy (CIPN), particularly in breast cancer patients treated with paclitaxel and colorectal cancer patients treated with oxaliplatin. This observational study assessed the efficacy of a dietary supplement, OnLife® (a patented mixture of specific fatty acids and PEA), in improving CIPN symptoms, with results showing that among patients receiving OnLife® treatment for 3 months after completing chemotherapy, 31.1% and 37.5% of breast cancer patients experienced improvements in peripheral sensory neuropathy (PSN) and peripheral motor neuropathy (PMN), respectively. In colorectal cancer patients, PSN and PMN improved in 16.9% and 20.0% of patients, respectively. Patient-reported outcomes indicated that 45.9% and 37.5% of patients with paclitaxel-induced PSN and PMN, respectively, and 23.9% and 22.0% of patients with oxaliplatin-induced PSN and PMN experienced alleviation of CIPN symptoms.[82]

A randomized, double-blind, placebo-controlled study on patients with neuropathic pain following spinal cord injury (SCI) investigated the effects of ultrafine powdered PEA (um-PEA) as an adjunct therapy, but the results showed that PEA-um did not demonstrate superior effects to placebo in reducing pain intensity, spasms, insomnia, or psychological function. Nevertheless, the study indicated that PEA did not lead to more adverse reactions compared to placebo.[83]

Dosage, Medication Regimen, and Evaluation of Long-Term Safety

PEA, as an endogenous substance, usually demonstrates good safety in clinical applications. However, further research is needed in terms of dosage, medication regimens, and long-term safety to optimize its use. Existing studies suggest that PEA may produce different efficacy at varying doses, and in some cases, high doses may lead to adverse reactions; therefore, determining the optimal dosage range is crucial.

The optimal dosage range for PEA varies across different studies. For example, in one study, elderly patients with chronic pain took 600mg of micronized PEA twice daily.[84] In another study, patients with neuropathic pain caused by spinal cord injury received micronized PEA as an adjunct therapy.[85] Additionally, there are studies using 10 mg/kg of PEA-m for postoperative analgesia.[86] These varying dosage regimens suggest that the optimal dosage of PEA may depend on the specific type of disease and patient characteristics.

Regarding the design of the medication regimen for PEA, current research mainly focuses on single or multiple administrations and duration, among other aspects. Some studies use short-term administration schemes, such as administering um-PEA before or after surgery in postoperative pain models.[86] In contrast, other studies employ long-term administration schemes, for instance, continuous administration of PEA for several weeks or even months in chronic pain patients.[84] These different administration schemes suggest that the efficacy of PEA may be influenced by the frequency and duration of administration.

The long-term safety of PEA is an important issue that needs to be addressed in clinical applications. Although PEA is generally considered to be safe, its effects on normal tissue organs (such as liver and kidney function) and potential adverse reactions still need to be assessed. Current studies indicate that PEA, as an endogenous substance, has lower toxic side effects,[87] but individual variability that may lead to different reactions still requires attention. A systematic

Table 2 The Clinical Trials of PEA in Cancer Chemotherapy-Related Side Effects (https://clinicaltrials.gov/)

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases	Study Type	Results
NCT03065478	Observational Study to Evaluate the Effectiveness of OnLife® in Improving CIPN in Patients With Colon or Breast Cancer After End of Adj. Therapy (STEFANO)	Completed	146 adult patients will be included. Cohort A: Adult patients with colon cancer(n=71) who experience CIPN after end of adjuvant oxaliplatin-containing chemotherapy; Cohort B: Adult patients with breast cancer (n=75) who experience CIPN after end of adjuvant paclitaxel chemotherapy	Dietary supplementation with "OnLife" (a patented fatty acid group (FAG) that comprises PEA, alpha-linolenic acid, eicosapentaenoic acid, (EPA), docosahexaenoic acid (DHA), linoleic acid, oleic acid, palmitic acid, stearic acid, arachidic acid and myristic acid). to improve signs and symptoms of CIPN in adult colon/breast cancer patients who experienced a CIPN after adjuvant oxaliplatin-containing chemotherapy. Interventions: Dietary Supplement: OnLife	/	Observational	OnLife® treatment is benefit for reducing CIPN severity and in limiting the progression of neuropathy, more markedly in paclitaxel-treated patients and also in patients with oxaliplatin-induced CIPN[82]
NCT05246670	PEA for the Relief of Chemotherapy-Induced Peripheral Neuropathy	Active, not recruiting	Chemotherapy-Induced Peripheral Neuropathy, Hematopoietic and Lymphoid Cell Neoplasm, Malignant Solid Neoplasm	Placebo Comparator: BID placebo Experimental: Higher-dose PEA, Experimental: Lower-dose PEA, Placebo Comparator: QD placebo	2	Interventional	PEA failed to improve established chemotherapy-induced neuropathy.[83]
NCT07022938	Nutritional Supplement for Treating Chemotherapy Induced Neuropathy	Completed	Cancer, Chemotherapy Induced Pain Neuropathy, Chemotherapy-Induced Peripheral Neuropathy, Neuropathy	Active Comparator: Epineuron: PEA, 300 mg, Superoxide Dismutase (SOD, 70 UI), Alpha Lipoic Acid (ALA, 300 mg), vitamins B6 (1.5 mg), B1 (1.1 mg), B12 (2.5 mcg), E (7.5 mg), Nicotinamide (9 mg) and minerals (Mg 30 mg, Zn 2.5 mg) in one tablet Placebo Comparator: Placebo tablet without active ingredients	4	Interventional	N/A

review shows that, compared to medical cannabis or cannabinoids, PEA is typically associated with few or no adverse events.[87] Nonetheless, future clinical trials must conduct a comprehensive evaluation of the long-term safety of PEA.

Delivery System of PEA and the Combination Therapy Strategies

New Drug Delivery System

PEA, as the multifunctional molecule, is commonly used in neuroprotection, chronic pain, and immune modulation and tumor regulation.[88,89] Nanocarriers is an important advancement in the field of tumor treatment, as it can precisely deliver drugs to tumor sites, increase local drug concentration, reduce systemic side effects, and thereby enhance therapeutic efficacy. The basic principle of nano-targeted delivery technology is to utilize the differences between tumor cells and normal cells to design carriers that can selectively recognize tumor cells, achieving specificity in targeting tumor tissues[90–93] (Figure 4A).

PLGA (poly (lactic-co-glycolic acid)) is a widely researched and applied biodegradable material that holds significant value in the field of drug delivery. The biocompatibility and biodegradability of PLGA make it an ideal drug carrier material. Eleonora Maretti et al,[94–96] reported hybrid nanoparticles combining poly (lactic-co-glycolic acid) (PLGA) and lipids can enhance PEA encapsulation, PEA-loaded hybrid nanoparticles (PEA-Hyb-np) were produced which provides a promising delivery platform to improve the solubility, bioavailability, and therapeutic efficacy of PEA for muscle-related inflammatory disorders. Meanwhile, Teresa Silvestri et al,[97] assessed the safety features of poly (lactic-co-glycolic acid) (PLGA)-based, hyaluronic acid-decorated microparticles loaded with PEA, which possessed a satisfactory safety profile in human retinal pigment epithelial (ARPE-19) cells. In vivo results also confirmed the safety profile of the loaded microparticles. These results suggested that the produced microparticles are promising for improving the local administration of neuroprotective molecules.

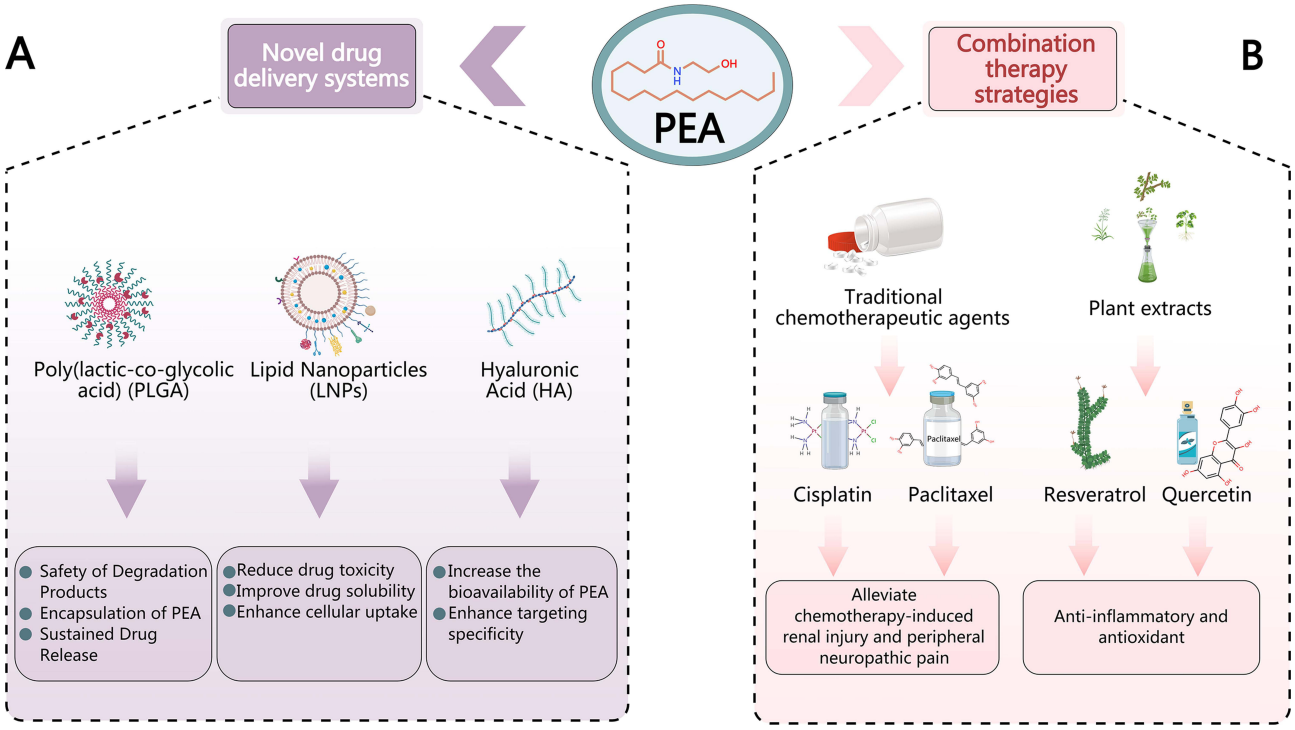

Figure 4 Improved strategies and applications of PEA. (**A**) Novel drug delivery system; (**B**) Combined treatment strategy.

Furthermore, Chuanpeng Ren et al,[98] reported that PEA-incorporated elastic nano-liposomes (PEA-ENL) exhibited the efficient transdermal delivery and enhanced skin retention, with negligible cytotoxicity toward HaCaT cells and no allergic reaction in the human skin patch test. Interestingly, PEA-ENL increased cell migration and induced significant regulation in the expression of genes associated with anti-nociceptive, anti-inflammatory, and skin barrier repair, showing multiple skincare functionalities.

Puglia et al,[99] reported that PEA loaded with nanostructured lipid carriers (NLCs) (PEA-NLCs) showed the high stability and robust ocular bioavailability. That was useful in clinical practice to manage retinal diseases.

In practical application cases, various nanoparticle carriers have been used for the delivery of PEA. Lipid nanoparticles increased PEA percutaneous diffusion and prolonged the anti-inflammatory and analgesic effects in vivo. Lipid nanoparticles seem a good nanotechnology-based strategy to bring PEA to clinics.[100]

Through targeted delivery, the local concentration of PEA at tumor sites can be significantly increased, reducing the distribution of the drug throughout the body, thereby enhancing bioavailability. Therefore, targeted delivery technology has broad application prospects in the tumor treatment of PEA.

Synergistic Effect of PEA and Conventional Chemotherapeutic Agents

The theoretical basis for the combined use of PEA with traditional chemotherapy drugs such as paclitaxel lies in the fact that PEA has multiple antitumor mechanisms and can produce a synergistic effect with chemotherapy drugs[101–104] (Figure 4B). PEA possesses various biological activities, including anti-inflammatory, anti-angiogenic, pro-apoptotic, and antioxidant properties, which can inhibit tumor growth and metastasis through different pathways.[62,75] Paclitaxel is commonly used chemotherapy drugs that primarily kill tumor cells by damaging DNA and interfering with cell division. However, prolonged use of chemotherapy drugs can lead to the development of drug resistance in tumor cells and cause serious side effects.[105–107] Oxaliplatin is a first-line chemotherapy drug for many cancers including breast cancer, ovarian cancer, and lung cancer, but it causes side effects such as peripheral neuropathic pain and acute kidney injury, chemoresistance, seriously affecting the chemotherapy process.[108–112] Co-administration of 2-pentadecyl-2-oxazoline of palmitoylethanolamide (PEA-OXA) acts on the NF-κB pathway, alleviating oxaliplatin-induced painful neuropathy.[113]

FAAH is the major catabolic enzyme for the endogenous lipid fatty acid amide family, capable of hydrolyzing lipid signaling molecules including anandamide (AEA), palmitoylethanolamide (PEA), oleoylethanolamide (OEA), and others.[114] FAAH knockout may protect against cisplatin-induced acute kidney injury by increasing the concentrations of PEA and OEA.[115] The combination of PEA and Polydatin significantly reduced the damage of doxorubicin and trastuzumab to human vascular endothelial cells by activating the PPAR-α pathway and inhibiting the NLRP3 inflammasome.[116] An earlier in vitro cellular study suggested that although PEA itself does not inhibit cell proliferation, it can significantly enhance the anti-proliferative effect of arachidonoylethanolamide on human breast cancer cells by inhibiting FAAH.[117]

Current research mostly focuses on the application of PEA in reducing side effects caused by chemotherapy drugs. By combining with PEA, the efficacy of chemotherapy drugs can be enhanced, the risk of resistance reduced, and side effects diminished.[101–104]

Combined Application of Plant Extracts

Many plant extracts have anti-cancer effects, such as resveratrol,[118] quercetin,[119] and Baicalein.[120–122] Currently, there is no direct research evidence showing that the combination of PEA and plant extracts can increase anti-tumor efficacy, but it still provides potential mechanisms and treatment options: Polydatin is a natural resveratrol glucoside derivative with various biological activities including anti-inflammatory, antioxidant and anti-cancer effects.[118,123–125] The combination of PEA and Polydatin can reduce the damage of chemotherapy drugs doxorubicin and trastuzumab on human vascular endothelial cells.[126] Endometriosis is a common chronic inflammatory gynecological disease, often accompanied by pelvic pain, dysuria, and other symptoms and is one of the risk factors for ovarian cancer, associated with a 50% increased risk of epithelial ovarian cancer.[127–129] The combination therapy of PEA and Polydatin not only relieved chronic pelvic pain in endometriosis but also led to varying degrees of reduction in endometriosis cysts in treated

patients.[130,131] This suggests that PEA and Polydatin may have therapeutic effects on endometriosis through mechanisms such as anti-inflammatory actions, potentially serving as a preventive treatment option for ovarian cancer.

Existing Challenges and Future Research Directions

In-Depth Discussion of Molecular Mechanisms and Signaling Pathways

Different Mechanisms of PEA in Tumor Types

PEA as an endogenous fatty acid amide has shown potential anti-tumor activity in various tumor models, but its mechanism of action varies significantly among different tumor types, providing important directions for future research (Figure 5).

In terms of breast cancer, research shows that PEA may play a role by regulating the expression of apoptosis-related genes. For example, Rai et al[64] found that PEA can alter the expression of apoptosis-related genes (Bax, P53, Bcl-XL, Caspase-8, and Caspase-9) in a DMBA induced breast tumor rat model, and induce the activity of Caspase-3 protein, thereby promoting tumor cell apoptosis. Additionally, in vitro studies have also demonstrated that PEA inhibited the secretion of IL-6 and IL-8, reduced the activation of NF-kB pathway, decreased the expression of VEGF and Placental growth factor (PLGF) in Triple-negative breast cancers (TNBCs), and inhibited tumor cell migration in vitro.[77]

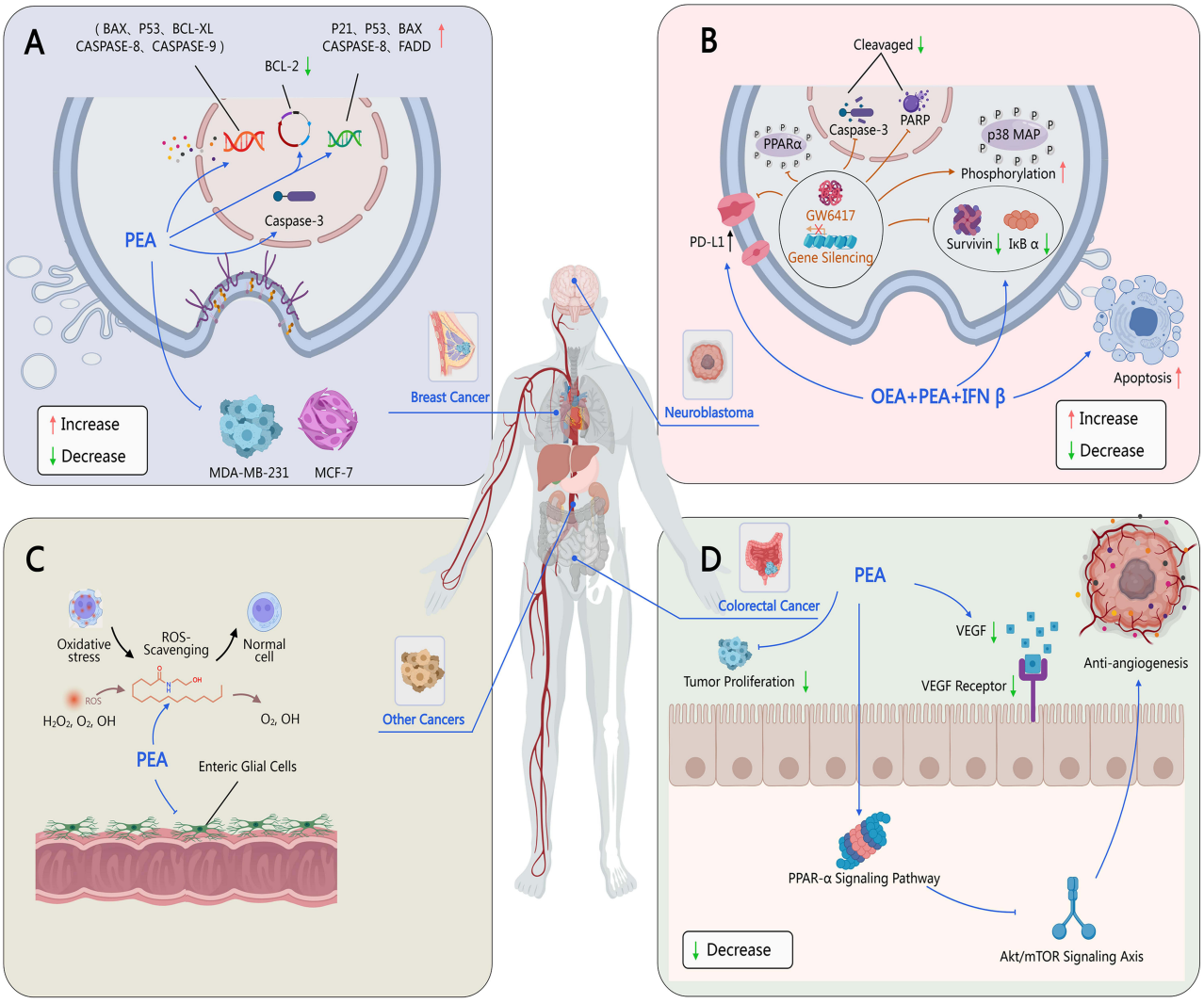

Figure 5 Heterogeneity studies of PEA in different tumors. (**A**–**D**) breast cancer, neuroblastoma, other tumors and colorectal cancer.

In colorectal cancer, the mechanism of action of PEA focuses on anti-proliferation and anti-angiogenesis. Sarnelli et al[62] found that PEA can concentration-dependently reduce the proliferation of Caco-2 human colon adenocarcinoma cells, decrease the secretion of VEGF, and reduce the expression of VEGF receptors. More importantly, PEA exerts its anti-angiogenic effects by specifically inhibiting the Akt/mTOR signaling axis through the activation of the PPAR-α pathway. These findings suggest that PEA may limit tumor growth in colorectal cancer by inhibiting the formation of tumor blood vessels. Besides, PEA suppressed the proliferation of CRC via PPAR-α and GPR55, induced G2/M arrest through upregulation of cyclin B1/CDK1. Moreover, PEA reduced MMP2 and TIMP1 expression to inhibit cell migration. In vivo study exhibited the beneficial effects of PEA in the azoxymethane mediated colonic tumors, through decreasing the number of precancerous lesions and tumors. These data provide the effects of PEA in colon carcinogenesis.[73]

In neuroblastoma cells, OEA (oleoyl-ethanolamide) and PEA interact with IFNβ to enhance apoptosis, leading to the cleavage of caspase 3 and PARP, while reducing the levels of survivin and IκBα. These lipids do not affect IFNβ signaling through the JAK-STAT pathway and STAT1-induced protein kinase R (PKR) but increase the phosphorylation of p38 MAP kinase and the expression of PD-L1 on the cell membrane. The use of the PPARα inhibitor GW6471 and gene silencing can reduce the levels of PD-L1 and cleaved PARP, revealing a new mechanism through which OEA and PEA can directly impair cell viability, proliferation, and colony formation ability by modulating and enhancing the intrinsic apoptotic pathways in human SH-SY5Y cells.[75]

Additionally, PEA has also shown different mechanisms of action in other tumor types. For example, in glioblastoma, PEA may exert neuroprotective effects by regulating inflammatory responses and oxidative stress.[71] In the diarrhea model induced by HIV-1 Tat protein, PEA is able to inhibit the activation of intestinal glial cells, thereby alleviating diarrhea symptoms.[132,133]

These studies indicate that the mechanisms of action of PEA exhibit significant heterogeneity across different tumor types. Therefore, future research needs to explore more in-depth the specific roles of PEA in various tumor microenvironments and develop more effective PEA treatment strategies targeting the characteristics of different tumors.

Cross-Regulation Among Various Signaling Pathways and Its Clinical Significance

The anti-tumor effect of PEA is not the result of a single pathway, but rather a complex network of multiple signaling pathways that interact and regulate each other. Understanding the interactions between these pathways is crucial for optimizing the therapeutic effects of PEA (Figure 6).

PPAR-α is one of the important targets through which PEA exerts its effects. Research by Sarnelli et al indicates that PEA can inhibit the Akt/mTOR pathway in Caco-2 cells by activating PPAR-α, thereby reducing the secretion of VEGF and angiogenesis. The Akt/mTOR pathway plays a crucial role in cell proliferation, growth, and survival, while VEGF is a key driver of angiogenesis. This finding reveals the molecular mechanism by which PEA regulates tumor angiogenesis through PPAR-α.

NF-κB is another signaling pathway closely related to the effects of PEA. Campolo et al found that PEA-OXA (2-pentyl-2-oxazoline) can alleviate oxaliplatin-induced neuropathy by modulating the NF-κB pathway. NF-κB is a key transcription factor involved in inflammatory responses and immune regulation. PEA-OXA relieves neuroinflammation and pain by inhibiting the activation of NF-κB and reducing the production of pro-inflammatory cytokines.[38,113]

Nrf2 is a key regulatory factor in cellular antioxidant defense. Research by Campolo et al also indicates that PEA-OXA can regulate the Nrf2 pathway and enhance the antioxidant capacity of cells. Nrf2 protects cells from oxidative stress damage by activating downstream antioxidant genes. PEA-OXA exerts neuroprotective effects by activating the Nrf2 pathway and alleviating oxidative damage caused by oxaliplatin. There is a complex interaction between inflammatory response and oxidative stress. The inflammatory response can promote the production of oxidative stress, while oxidative stress can exacerbate the inflammatory response. PEA can break this vicious cycle by simultaneously regulating the NF-κB and Nrf2 pathways, thereby exerting anti-tumor and neuroprotective effects.

The cross-regulation among these signaling pathways has important significance in clinical applications. For example, in CIPN, PEA can alleviate pain and neurological dysfunction by modulating the NF-κB and Nrf2 pathways, thereby reducing neuroinflammation and oxidative damage. A randomized, double-blind Phase II clinical trial by Davis et al

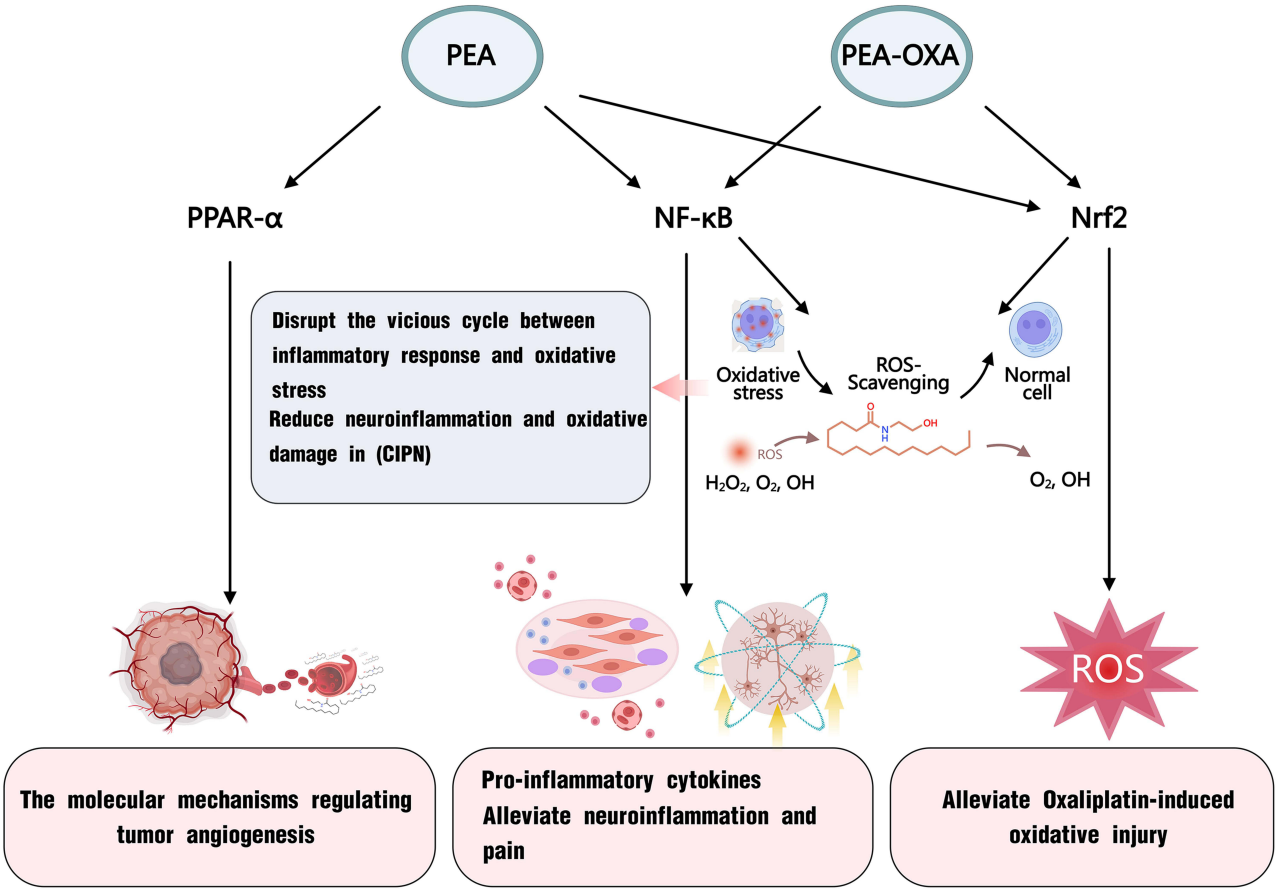

Figure 6 The cross anti-tumor effects of PEA.

indicated that PEA failed to improve diagnosed CIPN, but future trials could explore whether PEA can effectively prevent CIPN or cognitive changes. An observational study by Zaiss et al showed that OnLife® (a patented mixture of specific fatty acids and PEA) can improve CIPN symptoms in patients with breast cancer and colon cancer.

Understanding the main signaling pathways affected by PEA and their interactions can help develop more effective treatment strategies. For example, the combined application of PEA with chemotherapy drugs may enhance the anti-tumor effects through synergistic action while alleviating the side effects caused by chemotherapy. In addition, personalized PEA treatment based on patient genetic mutations, tumor types, and other characteristics may improve treatment outcomes.

Clinical Trial Design and Optimization

Necessity of Large-Scale, Multi-Center Randomized Controlled Trials

Currently, the clinical studies on PEA in cancer prevention and treatment are mostly small-sample, single-center trials, which limit the reliability and generalizability of the results (Table 2). There is an urgent need to conduct large-scale, multicenter randomized controlled trials to assess the efficacy and safety of PEA more comprehensively and objectively.

Large-scale trials can enhance statistical power, thereby allowing for a more accurate assessment of the therapeutic effects of PEA. Multicenter trials can include patients from different regions, ethnicities, and disease backgrounds, thus improving the representativeness and generalizability of the research findings. Randomized controlled trials can reduce selection bias and confounding factors, allowing for a more objective evaluation of the therapeutic effects of PEA.

In terms of research design, attention should be paid to the following points:

1. Clear inclusion criteria: Establish clear inclusion criteria to ensure that the included patients have similar disease characteristics and treatment needs.
2. Reasonable control group: Choose an appropriate control group based on the research purpose, such as a placebo group, standard treatment group, etc.
3. Standardized treatment plan: Develop a standardized PEA treatment plan, including dosage, administration method, course of treatment, etc.
4. Comprehensive efficacy evaluation: Use objective and reliable efficacy assessment indicators, such as tumor size, survival time, quality of life, etc.
5. Strict safety monitoring: Closely monitor patient safety and record the occurrence and severity of adverse reactions.

Personalized Treatment and Biomarker Development

Tumors are a highly heterogeneous disease, and different patients may react significantly differently to PEA. Therefore, personalized PEA treatment based on patient characteristics is of great importance.

Biomarkers are important tools for predicting a patient's response to PEA. By detecting biomarkers such as genetic mutations, tumor type, and immune status in patients, it is possible to identify those who are most likely to benefit from PEA treatment.

Some potential biomarkers have been identified. For example, the expression level of PPAR-α might predict the anti-tumor effect of PEA. The activity of the NF-κB and Nrf2 pathways may predict the efficacy of PEA against chemotherapy-induced peripheral neuropathy.

Future research should focus on developing more accurate and reliable biomarkers and integrating these biomarkers into clinical trials to optimize the therapeutic effects of PEA.

Improvement of the New Delivery System and Combination Therapy

Technical Strategies for Improving the Stability and Targeting of PEA

The bioavailability of PEA is relatively low, limiting its clinical applications. Therefore, developing new drug delivery systems to enhance the bioavailability and targeting of PEA is of significantly importance. Nanocarriers are a promising drug delivery system. For example, PLGA nanoparticles, lipid nanoparticles, and hyaluronic acid-modified microparticles can enhance the stability and bioavailability of PEA. Targeted delivery technology can concentrate PEA in the tumor locality, thereby enhancing efficacy and reducing systemic toxicity. For example, ADCs can selectively deliver PEA to tumor cells.

Research by Maretti et al indicates that it is feasible to prepare inhalable lipid nanoparticles (PEA-LNPs) using PEA. The study found that PEA-LNPs have good particle size and morphology and can significantly enhance the solubility of PEA. In vitro experiments show that PEA-LNPs are non-toxic to macrophages and can be rapidly engulfed by macrophages.

Optimization of Reasonable Dosage and Treatment Duration in Combination Therapy

The combination of PEA with other anticancer drugs may produce a synergistic effect, which can enhance the antitumor effect while reducing toxic side effects. The combination of PEA and conventional chemotherapy drugs (such as cisplatin and paclitaxel) has shown synergistic effects in some preclinical studies. PEA can also be combined with new drugs such as plant extracts and immune checkpoint inhibitors to explore new treatment strategies. In combined therapy, determining the appropriate dosage and treatment duration of PEA is crucial. A dosage that is too high may increase toxic side effects, while a dosage that is too low may fail to achieve the desired efficacy. A reasonable treatment duration can maximize efficacy while reducing the risk of resistance. Future research should be based on pharmacokinetic and pharmacodynamic data to develop individualized PEA dosing strategies and optimize combination therapy regimens to maximize efficacy and minimize side effects.

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PEA, as an endogenous molecule with multiple antitumor mechanisms, has broad application prospects in the field of tumor prevention and treatment. However, to achieve the clinical translation of PEA, many challenges need to be addressed, including in-depth studies of its molecular mechanisms, optimization of clinical trial designs, improvement of drug delivery systems, and exploration of reasonable combination therapy schemes. With continuous efforts, it is believed that PEA will play a greater role in tumor prevention and treatment in the future.

Conclusion

The Advantages of Comprehensive PEA Multiple Anti-Tumor Mechanisms

PEA, as an endogenous fatty acid amide, demonstrates synergistic advantages through multiple mechanisms in tumor prevention and treatment. PEA exerts anti-tumor effects through various pathways, including anti-inflammatory, anti-angiogenic, pro-apoptotic, and antioxidant actions. These mechanisms do not exist in isolation but coordinate with each other, collectively enhancing the effectiveness of tumor therapy. The multiple anti-tumor mechanisms of PEA give it significant advantages in clinical applications. It can not only directly inhibit tumor growth and spread but also improve patients' quality of life by regulating immunity and reducing toxic side effects, making PEA a potential adjuvant treatment for tumors.[134]

Small-scale clinical trials and case analyses have preliminarily validated the safety and efficacy of PEA. For example, a Phase II randomized double-blind trial for chemotherapy-induced peripheral neuropathy (CIPN) showed that PEA did not improve diagnosed CIPN, but the authors pointed out that, based on existing data, future trials could explore the efficacy of PEA in preventing CIPN or cognitive changes.[135] Another observational study indicated that OnLife® (a patented mixture containing specific fatty acids and PEA) improved CIPN symptoms in patients with breast and colon cancer.[82] Additionally, N-of-1 randomized trials also suggested that PEA has potential in controlling pain intensity and improving function in elderly patients with chronic pain.[83] Although the sample sizes of these trials are small, they lay the foundation for further large-scale studies.[82,83]

The research and application of PEA formulations are also constantly progressing. Currently, there are various PEA formulations available on the market, including standard PEA, um-PEA, and PEA analogs.[84,85,102] Ultra-micronization technology can improve the bioavailability of PEA, thereby enhancing its efficacy.[84,85] In addition, researchers are exploring different routes of administration, such as oral, local injection, and intravenous injection, to further improve the therapeutic effects of PEA.[88,97] Novel drug delivery systems, such as nano-carriers (PLGA, lipid nanoparticles, hyaluronic acid-modified microparticles), can enhance the bioavailability of PEA and achieve local tumor concentration and sustained release.[88–90]

Outlook on Future Personalized Precision Therapy and Combination Treatment Strategies

The application prospects of PEA in tumor prevention and treatment are broad, especially in personalized precision therapy and combination treatment strategies. In personalized therapy, future research should focus on adjusting the use of PEA based on the specific conditions of patients (such as tumor type, molecular markers, and genomic characteristics). For instance, PEA might be more effective for tumors with high expression of PPAR-α;[62,65] in tumor microenvironments with inflammatory responses, the anti-inflammatory effects of PEA may be more critical.[80,98,99] By screening biomarkers, it is possible to predict the patients' responses to PEA treatment, thereby achieving more precise treatment.[62,64,65]

Combination therapy is another important strategy for enhancing the efficacy of PEA. PEA can be used in conjunction with traditional chemotherapy drugs (such as cisplatin and paclitaxel) to enhance anti-tumor effects and reduce the risk of resistance.[62,97,102] Additionally, PEA can also be combined with novel drugs such as plant extracts and immune checkpoint inhibitors for a more comprehensive therapeutic effect.[75] When used in combination with immune checkpoint inhibitors, it can enhance the tumor immune response and improve treatment outcomes.[75] To realize the maximum potential of PEA in tumor prevention and treatment, larger-scale and multi-center clinical trials are still needed to optimize the use of PEA and develop more efficient combination therapy regimens. Future research should deeply

reveal the potential signaling pathways and biomarkers of PEA in combination with other drugs to guide clinical practice. At the same time, further studies are required to investigate the differences in the mechanisms of action of PEA in different tumor types, as well as the cross-regulation among various signaling pathways and their clinical significance.[62,64,65]

Collectively, PEA, as a natural molecule with multiple anti-tumor mechanisms, has great application potential in tumor prevention and treatment. Through the continuous optimization of personalized precision therapy and combination treatment strategies, PEA is expected to become an important component of future cancer treatments.

Abbreviations

ADCs, Antibody-drug conjugates; AOM, Azoxymethane; CAT, Catalase; Cb2, Cannabinoid type 2; CDKs, Cyclin-dependent kinases; CIPN, Chemotherapy-induced peripheral neuropathy; CTLs, Cytotoxic T cells; DMBA, 7,12-dimethylbenz[a]anthracene; GPR55, G protein coupled receptor 55; GSH-Px, Glutathione peroxidase; HA, Hyaluronic acid; HbT%, Average total hemoglobin; IFNβ, Interferon β; LNPs, Lipid nanoparticles; MDA, Malondialdehyde; NAAA, N-acylethanolamine acid amide hydrolase; NF-κB, Nuclear factor κB; NRF2, Nuclear factor erythroid 2-related factor 2; 8-OHdG, 8-hydroxydeoxyguanosine; PLGF, Placental growth factor; PPAR-α, Peroxisome proliferator-activated receptor α; ROS, Reactive oxygen species; SOD, Superoxide dismutase; sO2%, Average oxygen saturation; OEA, Oleoyl-ethanolamide; PARP, Poly-(ADP ribose) polymerase; PD-L1, Programmed cell death ligand 1; PEA, Palmitoylethanolamide; PEA-LNPs, Lipid nanoparticles; PEA-OXA, 2-pentyl-2-oxazoline; PLGA, Poly (lactic-co-glycolic acid); PKR, Protein kinase R; PSN, Peripheral sensory neuropathy; SCI, Spinal cord injury; Th cells, Helper T cells; Tregs, Regulatory T cells; um-PEA, Ultramicronized PEA; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Consent to Participate

This study did not involve human or animal subjects, and thus, no ethical approval was required. The study protocol adhered to the guidelines established by the journal.

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; Each author took part in drafting, revising or critically reviewing the article and gave final approval of the version to be published; We 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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