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REVIEW

# Palmitoylethanolamide in the Treatment of Pain and Its Clinical Application Prospects

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**Abstract:** Palmitoylethanolamide (PEA) has attracted increasing attention from researchers as an endogenous lipid mediator. It exhibits a unique mechanism of action in alleviating pain, controlling inflammation, and providing neuroprotection. It primarily regulates downstream signaling pathways by activating peroxisome proliferator-activated receptor alpha (PPAR-α) to inhibit the activity of nuclear factor kappa B (NF-κB), thereby reducing the production of pro-inflammatory cytokines. Additionally, PEA interacts synergistically with the endogenous cannabinoid system to modulate neurotransmission by enhancing the function of endogenous cannabinoids. The anti-inflammatory effects of PEA are also reflected in the regulation of glial cells and mast cells, effectively reducing local and central inflammation, thus protecting neuronal cells and promoting their regeneration. Clinical studies have shown that the application of PEA in various types of pain demonstrates good safety and tolerability, particularly suited for use in combination with traditional analgesics to enhance efficacy, reduce dependence, and minimize side effects. Despite existing research proving the effectiveness of PEA, challenges remain in its clinical promotion, including dosage form diversity, overall insufficient evidence, and patient individual differences. Therefore, future efforts should focus on strengthening multi-center large sample randomized controlled trials, coupled with biomarker investigations for personalized treatment research, to facilitate the widespread application of PEA in clinical pain management.

**Keywords:** palmitoylethanolamide, pain management, inflammation, neuroprotection, clinical applications

## Introduction

This chapter aims to introduce the multifactorial background of pain and inflammation from the perspectives of pathophysiology and molecular biology, while elucidating the fundamental characteristics of Palmitoylethanolamide (PEA), a natural lipid mediator, and its unique role in the regulation of inflammation and pain. It also discusses the limitations of current pain treatments and the potential advantages of natural medicines in terms of safety and tolerance, ultimately clarifying the purpose of this review and its interdisciplinary research perspective.

## Introduction to the Multifactorial Pathological Background of Pain

Chronic pain and neuropathic pain are common yet highly complex clinical problems, whose pathophysiological mechanisms involve multiple factors, various signaling pathways, and multi-level regulation[1,2] (Figure 1A). Pain generation, from peripheral to central, is regulated by a comprehensive array of mechanisms. Peripheral sensitization is primarily manifested under conditions of local tissue damage or inflammation, where inflammatory mediators (such as prostaglandins, interleukins, and other pro-inflammatory cytokines) released from the damaged area directly act on the nerve endings, significantly increasing the sensitivity of ion channels and receptors, thereby lowering the activation threshold and causing abnormal excitability. Meanwhile, central sensitization mechanisms also play a crucial role, where

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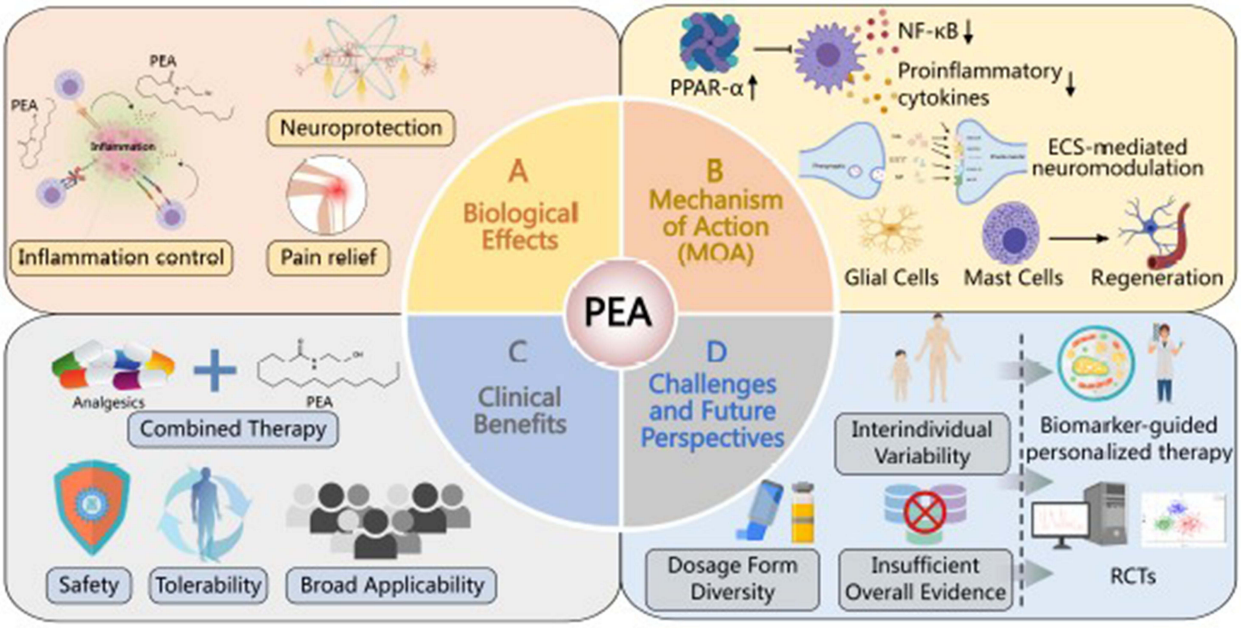
**Graphical Abstract**




persistent peripheral input stimuli lead to enhanced excitability of neurons in the spinal dorsal horn and higher-level central nervous system, along with changes in synaptic plasticity.[3,4] For instance, abnormal accumulation of neurotransmitters like glutamate in the synaptic cleft can activate N-methyl-D-aspartate (NMDA) receptors, triggering a cascade of signal transduction reactions that form neural adaptive changes such as long-term potentiation (LTP), further sustaining and amplifying pain signals.[5] In addition, structural changes of neurons, axonal regeneration, and synaptic remodeling following nerve injury are also significant factors contributing to the chronicity of pain, not only allowing pain signals to persist in the central nervous system for a long time but also posing challenges for subsequent pharmacological interventions.[6] Neuropathic pain, due to its origins often closely related to damage or pathological changes in the nerves themselves, is frequently accompanied by abnormal sensations such as tingling, burning, and electric shock-like feelings. This type of pain often shows inadequate response to analgesic treatments and requires special intervention measures to suppress pathological neuronal discharges and abnormal excitatory states.[7]

In the complex pain and inflammatory response, there exists a close and intricate interplay between the neuroendocrine and immune systems, and this network structure is considered a key factor in maintaining homeostasis and regulating the inflammatory response. Glial cells, including microglia and astrocytes, serve as important support cells in the central nervous system, and their roles in nerve injury, inflammation, and pain signal transmission have garnered increasing attention. (Figure 1B) After peripheral or central tissue injury, these glial cells are rapidly activated and secrete a large quantity of pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6), while they may also produce anti-inflammatory factors like IL-10, thereby participating in regulating the inflammatory process based on the varying local environmental conditions.[8] On the other hand, the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in regulating endocrine and immune balance during stress responses, with hormones released such as cortisol that can inhibit inflammatory responses to some extent;[9] however, in the context of long-term chronic pain, this balance is often disrupted due to excessive activation, further exacerbating local and systemic inflammatory conditions. Moreover, Jiang et al[10] reported that the activation of lymphocytes and monocytes in the immune system is also believed to be

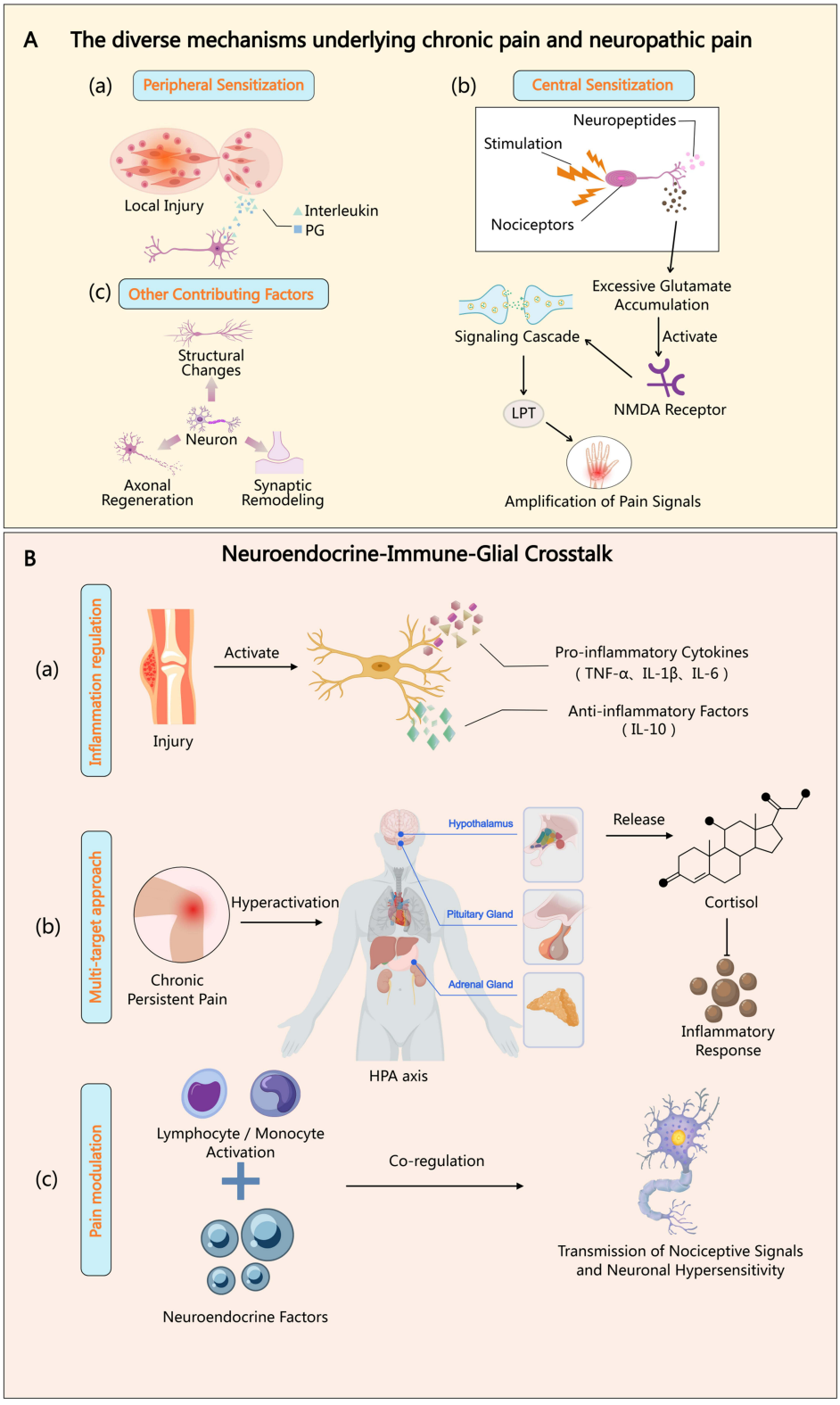



**Figure 1** The relevant mechanisms of pain and their interactions mediated by endocrine-immune-glial cells. (**A**) The diverse mechanism underlying chronic pain and neuropathic pain, including (a) peripheral sensitization, (b) central sensitization, (c) other contributing factors. (**B**) Neuroendocrine-immune-glial crosstalk in pain, including (a) inflammation regulation, (b) multi-target approach, (c) pain modulation.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closely intertwined with neuroendocrine factors, and together, they regulate the transmission of pain signals and the sensitivity of nerve cells, providing a multi-target and multi-pathway intervention strategy for pain treatment.

## Basic Properties of PEA

### Chemical Structure, Endogenous Production, and Exogenous Sources

PEA is an endogenous lipid mediator with a unique chemical structure, scientifically known as N-Palmitoylethanolamine.[5] Chemically, this molecule is composed of palmitic acid and ethanolamine, exhibiting certain lipophilicity and biological activity. PEA is primarily endogenously generated through the catalytic action of N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), while its degradation mainly relies on the action of N-acylethanolamine acid amidase (NAAA), thereby maintaining the balance level of PEA in the body. In addition to endogenous synthesis pathways, PEA can also be obtained from various natural foods such as egg yolks, soybeans, and peanuts, which provides the possibility to regulate the level of PEA in the body through diet[5,11,12] (Figure 2A). Currently, with the development of formulation technology, the metabolic kinetic characteristics of exogenously supplemented PEA have also received widespread attention. Novel formulation forms such as microparticle and ultra-microparticle forms can significantly improve its bioavailability, resulting in more ideal pharmacokinetic properties and therapeutic potential in clinical applications.

### The Unique Role of PEA in the Regulation of Pain

As a naturally occurring lipid mediator, PEA not only participates in regular cellular energy metabolism but is also known for regulating inflammatory responses and pain conduction (Figure 2B). Its uniqueness lies in being proposed as a "self-repair molecule"-a concept that emphasizes PEA's role in restoring homeostasis by activating specific receptors and regulating cytokine levels within the body. PEA exerts its anti-inflammatory effects primarily by PPAR-α, a pathway capable of inhibiting the activation of NF-κB and its downstream pro-inflammatory signaling, thereby alleviating inflammatory responses to some extent.[13] Additionally, PEA can indirectly modulate the endocannabinoid system through its "partner effect", enhancing the activity of substances like anandamide, which in turn reduces neuronal sensitivity to pain stimuli.[14] Furthermore, D'Aloia et al[15] reported that PEA has the significant effects in regulating the activity of glial cells; by attenuating the pro-inflammatory responses of microglia and astrocytes, it can effectively reduce

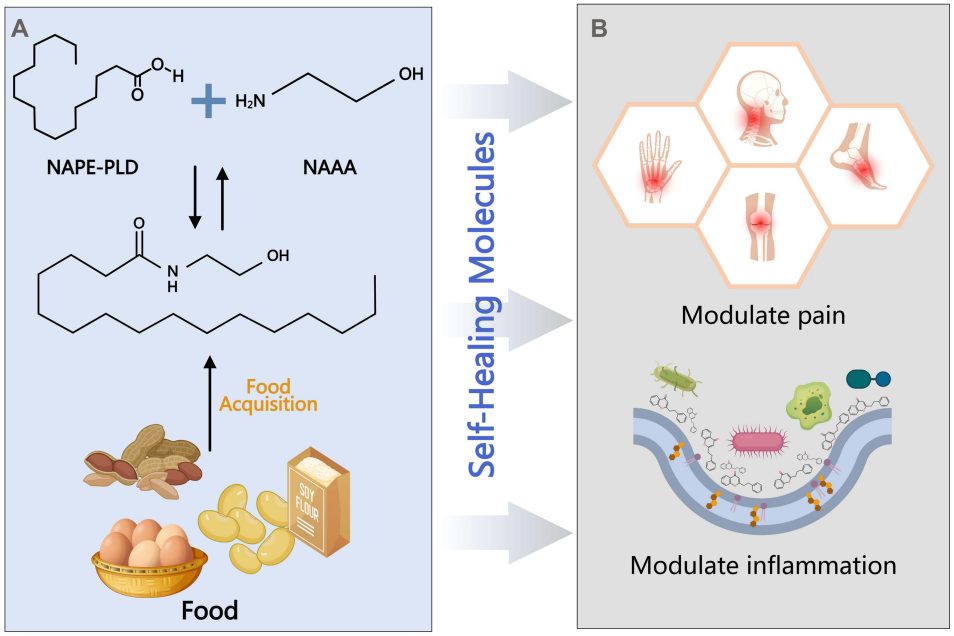


**Figure 2** Sources of PEA, synthesis methods, and its analgesic and anti-inflammatory effects. (**A**) The sources and synthesis methods of PEA. (**B**) The applications of PEA in pain and inflammation treatments.

local inflammation and associated pain signaling within the nervous system, providing a solid theoretical basis for its application in various inflammatory and neuropathic pain conditions.

## Limitations of Existing Treatment Methods and Advantages of Natural Medicines

Current traditional medications used for pain relief, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, do have certain effectiveness in analgesia; however, their widespread adverse reactions and tolerance issues have long been major concerns in clinical applications.[3,4] NSAIDs are often accompanied by gastrointestinal irritation, ulcers, and even cardiovascular side effects, while opioids carry risks of sedation, addiction, and tolerance, which pose significant challenges with long-term use.[3,4] In contrast, PEA, as an endogenous lipid mediator, has significant advantages in safety and tolerability. Numerous clinical studies have shown that within an appropriate dosage range, PEA not only exhibits notable anti-inflammatory and analgesic effects, but also has an extremely low incidence of adverse reactions, demonstrating good safety in special populations (such as the elderly and pregnant women). This high safety profile and broad therapeutic window make PEA suitable not only as a standalone therapy but also highly appropriate as an adjunct medication in combination treatments, reducing the dosage of main drugs and the associated risk of side effects.[16,17]

In addition to safety advantages, PEA also features multi-target and integrative regulatory characteristics in its analgesic mechanisms, demonstrating immense potential in replacing or assisting traditional analgesics. Firstly, PEA can directly intervene in multiple aspects of pain signal transmission and inflammatory responses by activating PPAR-α and regulating the endogenous cannabinoid system, thereby weakening the occurrence and maintenance of pain at the molecular level. Moreover, PEA has been shown to reduce the activation of glial cells and the release of pro-inflammatory cytokines; these mechanisms can exert analgesic effects independently and they also enhance efficacy when used in conjunction with other medications.[18,19] For instance, Déciga-Campos et al[20] reported that in the treatment of certain chronic neuropathic pain and fibromyalgia, the introduction of PEA can significantly decrease patients' dependence on opioids or other potent analgesics, thereby reducing the risks of drug tolerance and addiction; Simultaneously, its combination with other natural antioxidants or anti-inflammatory constituents can further enhance the overall analgesic effect and improve quality of life. This integrative multi-pathway regulatory paradigm provides new ideas and theoretical support for the future development of precision medicine and individualized treatment.[21,22]

## Overview of Objectives and Review of Research Status

### The Necessity of Integrating Clinical Data from Basic Mechanisms

Current research on pain and its related inflammatory responses has achieved a wealth of foundational results, but effectively translating these findings in molecular biology and cellular mechanisms into clinical practice still faces significant challenges. A large amount of basic and animal experimental data reveals the key roles of various cytokines, neurotransmitters, and receptors in the process of pain regulation, yet there remains a clear gap between these data and clinical trials. For example, while many studies indicate that PEA can effectively alleviate inflammation and neuropathic pain by inhibiting NF-κB, reducing pro-inflammatory cytokine levels, and regulating endocannabinoid-related signaling, there is still a lack of systematic integration regarding the specific mechanisms of action and optimal conditions in different pathological states.[23,24] Therefore, the primary goal of this review is to explore the effects of PEA in different pain models by consulting and integrating the latest clinical data, randomized controlled trials, as well as systematic reviews and meta-analyses, thereby providing a more comprehensive theoretical basis for the clinical translation of foundational research results, while also revealing current research shortcomings and new targets for further exploration in the future.

### Explanation of Article Structure and Interdisciplinary Perspectives

This article aims to provide readers with a systematic review of the mechanisms of action and clinical applications of PEA in pain relief. The structure of the article is designed to begin with the multifactorial pathological background of pain and inflammation, elaborating in detail on the pathogenesis of chronic pain and neuropathic pain at both peripheral and central levels, as well as the complex interactions between neuroendocrine, immune, and glial cells; secondly, it provides a comprehensive description of PEA's chemical structure, endogenous production, food sources, and its unique role as

a natural lipid mediator in the regulation of inflammation and pain processes; furthermore, it compares the significant differences in safety, tolerability, and multi-target regulatory mechanisms between traditional analgesics and PEA; finally, by integrating basic research and clinical data, it clearly points out the current knowledge gaps and bottlenecks that need to be addressed in the clinical translation process.[16,19] This article adopts a multidisciplinary perspective, incorporating neuroscience, immunology, pharmacology, and clinical medicine, aiming to provide a new theoretical framework and practical basis for the field of pain treatment. This interdisciplinary integration writing strategy not only helps readers recognize the complexity of pain generation and regulation from a macro to a micro perspective but also opens possibilities for developing individualized analgesic plans and exploring combination treatment strategies in the future. In summary, this article serves as a systematic review of existing literature, while also providing a solid foundation for future efforts to find new non-addictive analgesics and to facilitate the translation of basic research into clinical applications, with the hope of promoting more high-quality randomized controlled trials and multicenter large-sample studies to clarify the optimal dosing and administration routes of PEA, ultimately achieving the goal of precision medicine.

# The Mechanism of Action of PEA

## Molecular and Cellular Biological Mechanisms (Figure 3)

### Regulation of PEA and PPAR-α Activation and Downstream Signaling

PPAR-α is a nuclear receptor that plays an important role in the regulation of inflammation and pain. PEA, as an endogenous ligand of PPAR-α, can activate this receptor and initiate downstream signaling pathways.[20,25] PPAR-α and opioid receptors are involved in the interaction between PEA and morphine.[20]

PEA can regulate key signaling molecules such as NF-κB and p38-MAPK by activating PPAR-α. NF-κB is an important transcription factor involved in regulating the expression of various pro-inflammatory factors. PEA inhibits the activation of NF-κB through a PPAR-α dependent pathway, thereby reducing the release of pro-inflammatory factors and alleviating the inflammatory response.[26,27] p38-MAPK is another important signaling pathway involved in regulating neuroinflammatory responses. PEA can reduce neuroinflammatory responses and exert analgesic effects by modulating the activity of p38-MAPK.[28,29]

Both in vitro and in vivo studies have shown that PEA exerts anti-inflammatory and analgesic effects through the PPAR-α dependent pathway. For example, in animal models, PEA can alleviate inflammatory pain and neuropathic pain, and this effect can be blocked by a PPAR-α antagonist.[25,26]

### The Companion Effect of PEA and the Endogenous Cannabinoid System

The endogenous cannabinoid system (ECS) consists of CB1 and CB2 receptors and their endogenous ligands such as N-arachidonoylethanolamine (AEA), playing a significant role in pain and inflammation. The interaction of PEA with ECS does not directly activate CB1/CB2 receptors but achieves the "entourage effect" by indirectly regulating ECS.[30]

The "entourage effect" of PEA is mainly reflected in its inhibition of the enzyme fatty acid amide hydrolase (FAAH) that degrades endogenous cannabinoids, thereby increasing the levels of endogenous cannabinoids such as AEA and prolonging their action.[31] Since AEA can activate CB1 and CB2 receptors, PEA indirectly enhances the activity of the ECS by increasing the levels of AEA, thus alleviating pain and inflammation.[25]

The synergistic effect of PEA and ECS can relieve pain and inflammation together, while avoiding the side effects of traditional cannabinoids, such as psychoactive effects.[32] In animal models and clinical studies, the interactions between PEA and ECS have demonstrated good analgesic and anti-inflammatory effects.[33] For example, Mabou Tagne et al[34] reported that the combination of PEA with hempseed oil extract showed a synergistic anti-hyperalgesic effect in mouse models of acute and chronic pain. Pharmacokinetic experiments indicate that co-administration of HOE can enhance and prolong the systemic exposure of PEA.

### Regulation of the Activation of Glial Cells

Microglia and astrocytes are important glial cells in the central nervous system, playing a key role in chronic pain and neuroinflammation. In the state of chronic pain and neuroinflammation, these glial cells become overactivated, releasing a large amount of pro-inflammatory cytokines, exacerbating neuroinflammation and central sensitization.

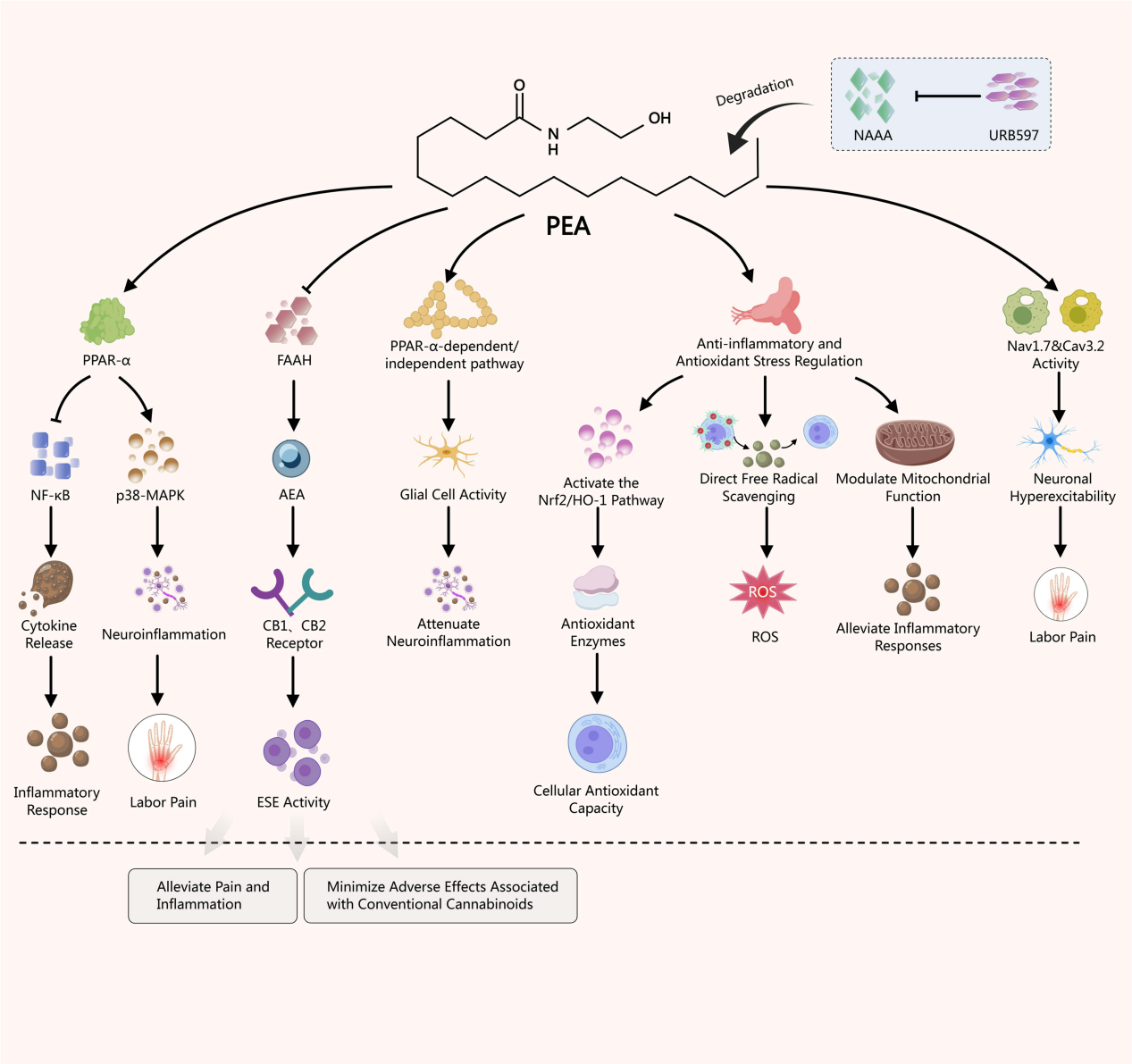


**Figure 3** The specific regulatory mechanism of PEA on pain relief. PEA can alleviate pain and inflammation, as well as minimizing adverse effects associated with conventional cannabinoids.

PEA can alleviate neuroinflammation and central sensitization by inhibiting the excessive activation of glial cells. PEA reduces the release of pro-inflammatory cytokines such as IL-1β and TNF-α, thereby alleviating neuroinflammation.[32] The specific signaling pathways through which PEA regulates glial cell activation include PPAR-α-dependent and non-dependent pathways, such as the TLR4/NF-κB pathway.[25,26] In the spinal cord, PEA reduces inflammation, oxidative stress, and p38-MAPK activity.[28,29]

Both animal models and cell experiments show that PEA has a good regulatory effect on the activation of glial cells. For example, in a spinal cord injury model, PEA can reduce the activation of microglia and astrocytes in the spinal cord, alleviating neuroinflammation and thus relieving neuropathic pain.[35]


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## Neuroprotective and Metabolic Regulatory Effects

### Mechanisms of Antioxidant Stress and Anti-Inflammatory Regulation

Oxidative stress, such as the accumulation of reactive oxygen species (ROS), plays an important role in neuropathic pain and chronic inflammation. ROS can damage nerve cells, exacerbate inflammatory responses, and lead to increased pain.[36,37]

PEA has an antioxidant effect and can enhance antioxidant defenses through multiple mechanisms. PEA can activate the Nrf2/HO-1 pathway, upregulate the expression of antioxidant enzymes, and enhance the antioxidant capacity of cells. In addition, PEA can also directly scavenge free radicals and reduce the accumulation of ROS.[38]

In addition to its antioxidant effects, PEA also has anti-inflammatory and metabolic regulatory functions. PEA can regulate mitochondrial function, improve energy metabolism, and block the vicious cycle of inflammation-oxidative stress. For example, PEA affects mitochondrial respiration, mitochondrial membrane potential, and ROS production. PEA improves cellular energy metabolism by regulating the AMPK pathway, thereby alleviating inflammatory responses.[36]

### Effects on Ion Channels, Neurotrophic Factors, and Synaptic Plasticity

PEA regulates various ion channels, including voltage-gated sodium channels and calcium channels. PEA can modulate the activity of ion channels such as Nav1.7 and Cav3.2, thereby inhibiting the hyperexcitability of neurons and exerting an analgesic effect.[39] Through interaction with the Nav1.7 channel, PEA can directly affect sensory neurons and pain transmission.

Brain-derived neurotrophic factor (BDNF) is an important neurotrophic factor that plays a key role in neural repair and synaptic plasticity. PEA can upregulate the expression of BDNF, promoting neural repair and synaptic plasticity, and reversing synaptic remodeling associated with chronic pain.[25] Under chronic pain conditions, synaptic plasticity is altered, leading to the abnormal transmission and amplification of pain signals. By regulating synaptic plasticity, PEA can restore normal neural function and reduce pain.

In experiments on animal behavior, PEA improves pain behavior and neurological functions through mechanisms such as regulating ion channels and upregulating BDNF expression.[40] PEA treatment alleviates pain and cognitive impairments, thereby restoring LTP and maladaptive changes in synapses within the LEC-DG pathway.[25]

## Relevant Molecular Targets and Novel Regulatory Pathways

### Regulation of Endogenous PEA Levels by NAAA and Its Inhibition

NAAA is an intracellular lysosomal enzyme responsible for the degradation of PEA, thereby regulating the levels of PEA in the body. The pathological significance of NAAA in pain lies in its excessive activation, which can lead to a decrease in PEA levels, thereby weakening endogenous analgesic and anti-inflammatory effects.[41,42]

By inhibiting NAAA, the endogenous levels of PEA can be increased, enhancing its analgesic and anti-inflammatory effects. For example, URB597 is an NAAA inhibitor that exerts its analgesic effect by increasing endogenous PEA levels. Compared to the administration of exogenous PEA, inhibiting NAAA has certain advantages, as it can more precisely regulate PEA levels and may reduce side effects.[42]

### Schematic and Integration of Multi-Target Synergistic Action Pathways

The mechanism of action of PEA involves multiple targets, including PPAR-α, ECS, glial cells, and ion channels.[43] These targets interact to form a complex regulatory network that collaboratively exerts analgesic, anti-inflammatory, and neuroprotective effects.

From the perspective of network pharmacology, PEA has the characteristic of "systemic regulation" and can exert effects through multiple pathways in a collaborative manner. This multi-target synergistic effect is one of the advantages of PEA, which can overcome the limitations of single-target drugs. In contrast, single-target drugs may only focus on a specific pathway or target, while PEA can modulate multiple pathways and targets to more comprehensively intervene in the pathological processes of pain and inflammation.[43]

# Clinical Applications

## Current Status of Clinical Research on Different Pain Types (Table 1)

### Clinical Trials and Analysis of Chronic Pain and Neuropathic Pain

Chronic pain and neuropathic pain are common conditions affecting millions of people worldwide, significantly reducing the quality of life for patients. Traditional treatment methods often have limited effectiveness and are accompanied by significant side effects; therefore, the search for safer and more effective alternative therapies has become an urgent necessity.

In the treatment of fibromyalgia, PEA has shown certain potential. Several clinical trials have assessed the effect of PEA on pain relief in patients with fibromyalgia, with study designs including randomized controlled trials and double-blind trials, varying sample sizes, and differences in PEA dosage and duration of treatment. The primary outcome measures typically involve pain scoring, such as the Visual Analog Scale (VAS). Salaffi et al[44] conducted a randomized controlled study examining the efficacy of adding PEA and Acetyl-L-Carnitine (ALC) in fibromyalgia patients receiving stable treatment with Pregabalin (PGB) and Duloxetine (DLX). The results indicated that after 24 weeks of treatment, patients receiving the combination of PEA+ALC showed significant improvements in the Widespread Pain Index (WPI), Fibromyalgia Impact Questionnaire-Revised (FIQR), and modified Fibromyalgia Assessment Status (FASmod) score compared to those receiving only DLX+PGB treatment.

Low back pain is another common type of chronic pain that severely affects patients' quality of life and work ability. Scaturro et al conducted an observational study to assess the effectiveness of ultra-micronized PEA (umPEA) combined with CAM (daily functional rehabilitation + relaxation massage) in treating chronic low back pain caused by multiple lumbar disc herniations.[45] The results indicated that the average pain intensity score, assessed by a numerical rating scale, gradually decreased during the study period, reaching a clinically irrelevant level by the end of the observation period.[45] Pain relief was accompanied by improvements in both the physical and mental components of quality of life, as well as improvements in low back disability measured by the Oswestry Disability Questionnaire.

Chemotherapy-induced neuropathic pain (CIPN) is a common side effect of cancer treatment that severely impacts patients' quality of life. The research by Elfarnawany and Dehghani[46] suggests that PEA may alleviate the toxicity of paclitaxel to dorsal root ganglion (DRG) neurons. This study utilized primary DRG neurons as a model to investigate the potential neuroprotective effects of PEA. The findings indicated that the adverse effects of paclitaxel on cell viability emerged 72 hours post-treatment, and the neurite length was significantly reduced in a concentration-dependent manner at nearly all study time points. However, paclitaxel significantly increased the size of neuronal cell bodies across all time windows. In neurons additionally treated with PEA, these phenotypic effects were significantly reduced, indicating that PEA exhibits neuroprotective properties.[46]

Some meta-analyses have summarized the efficacy of PEA in chronic pain and neuropathic pain. Paladini et al[47] conducted a pooled data meta-analysis to assess the efficacy and safety of micronized and ultra-micronized PEA for patients with chronic and/or neuropathic pain. The meta-analysis included 12 studies, and the results showed that PEA could gradually reduce pain intensity compared to the control group, and that the effects of PEA were independent of the patients' age or sex, as well as unrelated to the type of chronic pain.[47]

These clinical trial and meta-analysis results indicate that PEA has certain potential in the treatment of chronic pain and neuropathic pain, but more high-quality clinical studies are needed to verify its efficacy and safety.

### Preliminary Clinical Data on Osteoarthritis, Sciatica, Pelvic Pain, and Other Types of Pain

In addition to chronic pain and neuropathic pain, PEA also shows certain potential for application in the treatment of other types of pain such as osteoarthritis, sciatica, and pelvic pain.

In terms of osteoarthritis, a study by Britti et al[48] found that the combined use of PEA with the natural antioxidant quercetin (PEA-Q) can reduce inflammation and osteoarthritis pain. In animals treated with MIA, PEA-Q had the following effects: (i) reduced mechanical allodynia and improved motor function, (ii) protected cartilage from MIA-induced histological damage, and (iii) offset the increased concentrations of tumor necrosis factor α, interleukin 1 β, metalloproteinases 1, 3, 9, and nerve growth factor in serum.

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**Table 1** The Clinical Applications of PEA in Pain Treatment

| NCT.NO | Title | Status | Company Name | Conditions | Study Record Dates | Enrollment | Study Plan | Results | Phase |
|---|---|---|---|---|---|---|---|---|---|
| NCT01491191 | Palmitoylethanolamide for Post-operative Pain Prevention (PEAforCPSP) | Unknown status | University of Modena and Reggio Emilia | Chronic Post-operative Pain | 201201-201307 | 300 | Participants were put into groups. Group A received PEA before and after surgery, Group B received Placebo. | N/A | Not Applicable |
| NCT05406726 | Mechanisms of Palmitoylethanolamide (PEA) to Alter Pain Sensitivity in Knee Osteoarthritis | Completed | University of Maryland, Baltimore | Osteoarthritis, Knee | 202303-202401 | 13 | This is a crossover clinical trial where 10 participants will receive PEA dietary supplement for 6 weeks and 10 participants will receive placebo for 6 weeks. Then the following 6 weeks they will reverse. | N/A | Not Applicable |
| NCT02699281 | Efficacy of Ultra-micronized Palmitoylethanolamide (Um-PEA) in Geriatric Patients With Chronic Pain | Completed | Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico | Chronic Pain | 201510-201607 | 11 | Experimental: Ultra-micronized PEA 600 mg twice a day. Placebo Comparator: Placebo twice a day. | N/A | 4 |
| NCT05480072 | Endocannabinoids, Stress, Craving And Pain Effects Study (ESCAPE) | Recruiting | Brigham and Women's Hospital | Opioid Use Disorder | 202211-202412 | 16 | Active Comparator: PEA capsules (600 mg twice a day) will be administered for 21 days. Placebo Comparator: Placebo capsules (600 mg twice a day) will be administered for 21 days | N/A | Early 1 |
| NCT05317676 | Effect of Palmitoylethanolamide on Reducing Opioid Consumption for Below Knee Fracture Fixation | Withdrawn | University of California, Irvine | Fibula Fracture Knee Fracture Tibial Fractures | 202305-202512 | 0 | Active Comparator:300 mg PEA twice a day for a total of 600 mg PEA daily 2-month supply upon discharge. Placebo Comparator: 1 placebo tablet twice a day for a total of 2 tablet placebo daily 2-month supply upon discharge. | N/A | 2 |
| NCT06273462 | Palmitoylethanolamide for Chronic Inflammatory Pain Conditions | Recruiting | Navy Medical Center San Diego | Chronic Pain | 202408-202510 | 80 | Prospective Randomize Double Blind Placebo Controlled study comparing the supplement PEA to a visually identical placebo. | N/A | 2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NCT06694337 | Study to Investigate the Potential Pharmacological Effect of Oral Palmitoylethanolamide (PEA) Therapy in the Management of Low Back Pain (Neuropathic Pain) | Active, not recruiting | Liaquat University of Medical & Health Sciences | Low Back Pain | 202501-202506 | 120 | Experimental: 300 mg PEA group. Experimental: 450 mg PEA group. Placebo Comparator: Control group. | N/A | Not Applicable |
| NCT02372903 | Efficacy of Palmitoylethanolamide-polydatin Combination on Chronic Pelvic Pain in Patients With Endometriosis | Completed | University of Cagliari | Chronic Pelvic Pain Endometriosis | 201310-201509 | 30 | Experimental: Endometriosis. PEA 600 mg twice daily for 10 days sublingually and oral PEA 400 mg and polydatin 40 mg, twice daily for 90 days | N/A | Not Applicable |
| NCT05046522 | A Study Evaluating the Effectiveness of PEA Compared to Placebo for Reducing Pain Severity and Duration of Migraines. | Completed | RDC Clinical Pty Ltd | Migraine | 202109-202303 | 80 | Experimental: PEA sold as Levagen +Placebo Comparator: A comparator placebo capsule - Maltodextrin and microcrystalline cellulose mix | N/A | 3 |
| NCT04662827 | The Effect of Palmitoylethanolamide on Central and Peripheral Sensitization After Heat-induced Hyperalgesia | Completed | Medical University of Graz | Pain, Acute Pain, Chronic Central Sensitisation Neuroinflammatory Response | 202002-202009 | 14 | Experimental: Probands receive PEA 3xday for 28 days, 8 weeks wash out will follow, then they receive placebo for 28 days. Placebo Comparator: Probands receive placebo 3xday for 28 days, 8 weeks washout will follow, then they receive PEA for 28 days | N/A | Not Applicable |
| NCT05877170 | Impact of Palmitoylethanolamide (PEA) in the Management of Oro-facial Pain | Recruiting | University of Catania | Oral-facial Pain | 202002-202308 | 40 | Experimental: PEA-containing nutraceutical agent in oral formulation. Placebo Comparator: Patients treated with a placebo. | N/A | Not Applicable |

(*Continued*)

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**Table 1** (Continued).

| NCT.NO | Title | Status | Company Name | Conditions | Study Record Dates | Enrollment | Study Plan | Results | Phase |
|---|---|---|---|---|---|---|---|---|---|
| NCT04488926 | Micronized and Ultramicronized Palmitoylethanolamide in Fibromyalgia Patients | Completed | Epitech Group SpA | Fibromyalgia | 202007-202205 | 21 | Group 1: Normast® MPS (mPEA and umPEA 300mg + 600mg) microgranules for sublingual use, 1800mg/die in 2 doses (morning and evening) for 90 days. Group 2: Placebo microgranules for sublingual use, 1800mg/die in 2 doses (morning and evening) for 90 days | N/A | 4 |
| NCT05810116 | Effectiveness of PEA Compared to Placebo on Acute Menstrual Pain | Completed | RDC Clinical Pty Ltd | Menstrual Pain | 202305-202312 | 80 | Active Comparator: Levagen+ Daily dose of 1–2 capsules (1 capsule containing 350mg Levagen+ equivalent to 300mg PEA). Placebo Comparator: Microcrystalline cellulose Daily dose of 1–2 capsules (1 capsule containing 350mg) | N/A | 4 |
| NCT04091789 | Sublingual Tablets With Cannabinoid Combinations for the Treatment of Dysmenorrhea | Unknown status | Pure Green | Dysmenorrhea Fatigue Headache, Migraine Mood Disturbance Nausea | 201909-202005 | 30 | Subjects will take Pure Femme sublingual tablets as directed, one tablet 2 days before, one tablet 1 day before, and then up to 3 tablets per day for 3 days (72 h) during menstruation. | N/A | 2 |
| NCT05766969 | Diabetic Neuropathic Pain Relief, 6 Weeks Dosage Sublingual Water-soluble CBD/PEA | Unknown status | Pure Green Pharmaceuticals Inc. | Diabetic Peripheral Neuropathic Pain | 202306-202312 | 52 | Subject will receive a 42-day supply of 10/50 mg CBD/PEA sublingual tablets to be taken 3 times a day for 42 days. A placebo sublingual tablet to be taken three times a day for 42 days. | N/A | 1 and 2 |
| NCT05753111 | Effect of PEA on Muscle Recovery Following Resistance Exercise | Completed | KU Leuven | Muscle Recovery Muscle Soreness | 202302-202305 | 11 | Placebo Comparator: Placebo. Experimental: PEA supplementation | N/A | Not Applicable |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NCT01851499 | Ultramicronized PEA (Normast) in Spinal Cord Injury Neuropathic Pain | Completed | Danish Pain Research Center | Neuropathic Pain Spinal Cord Injury | 201305-201510 | 73 | Experimental: Ultramicronized PEA (Normast). Placebo Comparator: Microgranules | N/A | Not Applicable |
| NCT05984771 | Efficacy and Safety of the Combination of Ten Elements for 6 Months in Patients With Diabetic Neuropathy: A Pilot Study | Completed | Aristotle University Of Thessaloniki | Diabetes Mellitus Diabetic Neuropathies Dietary Supplement | 202101-202206 | 70 | Active Comparator: Superoxide Dismutase (SOD, 70 UI), PEA (300 mg), 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 (Epineuron). | N/A | Not Applicable |
| NCT05357157 | Electroacupuncture Pain Treatment, Mechanical Hyperalgesia, Quality of Life & Expression of Mu+ B Cells in Fibromyalgia | Recruiting | University of Crete | Acupuncture Electroacupuncture Fibromyalgia Hyperalgesia | 202205-202612 | 80 | Placebo Comparator: Placebo Electroacupuncture. Electroacupuncture, Nutrition and Dietary supplement | N/A | Not Applicable |


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In the context of sciatica, Bonetti et al[48] conducted an observational study comparing the efficacy of oxygen-ozone therapy combined with oral α-lipoic acid (ALA) + PEA and myrrh against ozone therapy alone for treating sciatica caused by herniated discs. The results indicated that, during clinical examination, out of 165 patients in Group A (who received only oxygen-ozone therapy), 126 patients completely relieved their pain (76.4%), whereas in Group B (who received oral treatment with ALA + PEA and myrrh), 119 out of 153 patients completely relieved their pain (77.8%).[48]

In terms of pelvic pain, Tafuri et al conducted an in vitro study to evaluate the efficacy of a patented formulation (Pelvipea®) composed of micronized PEA, hemp seed oil, and dried extract of maritime pine bark, aimed at reducing urothelial inflammation.[49] The in vitro bladder urothelial model consisted of T24 cell lines exposed to conditioned media obtained from THP-1 cells differentiated by treating them with various concentrations of functional ingredients and their mixtures in the presence of pro-inflammatory stimuli from Escherichia coli.[49] The results indicated that the mixture of micronized PEA, hemp seed oil, and dried extract of maritime pine bark (Pelvipea®) showed optimal efficacy in reducing urothelial IL-1β, IL-6, and IL-8 at a concentration of 230 μg/mL compared to single functional ingredients.[49] Cervigni et al[50] conducted a preliminary open-label multicenter study assessing the impact of a product based on micronized-PEA-Polydatin (m-PEA-Pol) on the severity of chronic pelvic pain and other symptoms observed in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) resistant to conventional therapies.[28] The results showed that during m-PEA-Pol treatment, a significant and gradual decrease in pain intensity was observed.[50] This effect was associated with a reduction in the severity of symptoms assessed through the O'Leary-Sant questionnaire and the PUF scale.[50]

Morgia et al[32] conducted a clinical study aimed at evaluating the efficacy of PEA, willow herb, and marigold extract in treating patients with CP/CPPS type III. The results indicated that after one month of treatment, there were statistically significant improvements in NIH-CPSI, U-WBC, PSA, IIEF-5, peak flow rate, PVR, and VAS.

Although these preliminary data offer hope for the use of PEA in other types of pain, the current research still has some limitations, such as small sample size and lack of long-term follow-up. Therefore, more high-quality clinical trials are needed to validate the efficacy of PEA in these types of pain.

## PEA as an Adjunct or Combination Therapy

### Synergistic Effects When Used in Combination with Traditional Analgesics

As an endogenous lipid mediator, PEA has anti-inflammatory and analgesic effects, and it is relatively safe. Combining it with traditional analgesics may produce a synergistic effect, thereby enhancing efficacy and reducing the dosage and side effects of conventional drugs.

From a molecular mechanism perspective, PEA may synergistically enhance the effects of traditional analgesics through different pathways. For example, PEA can enhance anti-inflammatory effects by activating the PPAR-α receptor, reducing the release of inflammatory mediators, thereby enhancing the analgesic effects of NSAIDs. At the same time, PEA can also modulate the endocannabinoid system, affecting the transmission and perception of pain signals, thereby enhancing the analgesic effects of opioids.

Some clinical studies have confirmed the synergistic effects of PEA when used in combination with traditional analgesics. For example, some research indicates that PEA can reduce the dosage of opioids, thereby decreasing side effects such as constipation and nausea. Additionally, PEA can also reduce gastrointestinal, liver, and kidney toxicity caused by NSAIDs.

Peritore et al[51] studied the neuroprotective effects of a new combination of ultra-micronized palmitoylethanolamide (PEAum) and paracetamol in a rat model of sciatic nerve injury (SNI). The combination of PEAum and paracetamol was able to reduce hyperalgesia, mast cell activation, c-Fos and nerve growth factor (NGF) expression, neuronal histological damage, cytokine release, and cell apoptosis. Furthermore, the analgesic effect of PEAum and paracetamol may act synergistically by inhibiting the NF-κB pathway, thereby reducing the release of cyclooxygenase-2 dependent prostaglandin E2 (COX-2/PGE2).[51]

Nobili et al[52] provided a comprehensive review of ultrafine powdered PEA, with data showing that ultrafine powdered PEA has the ability to limit the side effects of opioids, including the development of tolerance.

These studies indicate that the combined use of PEA with traditional analgesics can produce a synergistic effect, enhancing efficacy and reducing side effects, thereby providing a new option for the treatment of chronic pain.

## Combined Treatment Cases with Other Natural Antioxidants

In addition to being used in conjunction with traditional analgesics, PEA can also be combined with other natural antioxidants and anti-inflammatories to achieve a more comprehensive therapeutic effect. These natural components may have a complementary effect with PEA, such as synergistic antioxidant and mitochondrial protection.

Alpha-lipoic acid is a potent antioxidant that can eliminate free radicals, reduce oxidative stress, and protect nerve cells from damage. L-carnitine can promote the metabolism of fatty acids, provide energy to nerve cells, and improve nerve function. The combined application of PEA with natural ingredients such as alpha-lipoic acid and L-carnitine can synergistically exert antioxidant effects, protect nerve cells, and alleviate pain.

Didangelos et al[53] studied the efficacy of PEA (300 mg), superoxide dismutase (SOD, 70 UI), alpha-lipoic acid (ALA, 300 mg), vitamin B6 (VB6, 1.5 mg), VB1 (1.1 mg), VB12 (2.5 mcg), VE (7.5 mg), niacinamide (9 mg), and minerals (Mg 30 mg, Zn 2.5 mg) in patients with diabetic neuropathy (DN). The results indicated a significant improvement in pain (PS decreased from 20.9 to 13.9, $p < 0.001$) in the active group. Levels of VB12, MNSIQ, SNCV, VPT, and ESCF also showed significant improvement.

Infantino et al[54] found that repeated administration of co-supramolecular PEALut significantly reduced mechanical hypersensitivity after thalamic hemorrhage (TH) in a CPSP mouse model, and this was associated with reduced early microglial activation in the lesion surrounding area. Additionally, PEALut prevented the development of depressive-like behavior (21 days post-TH). These effects are related to the restoration of synaptic plasticity in the LEC-DG pathway and the impaired monoamine levels observed in TH mice.

Salaffi et al[44] conducted a randomized controlled trial to investigate the efficacy of adding PEA and acetyl-L-carnitine (ALC) in fibromyalgia patients receiving stable treatment with pregabalin (PGB) and duloxetine (DLX). The results showed that after 24 weeks of treatment, patients receiving the combination of PEA and ALC had significant improvements in WPI, FIQR, and FASmod scores compared to those receiving only DLX + PGB treatment.

These cases indicate that the combined application of PEA with other natural antioxidants and anti-inflammatory agents can produce a more comprehensive therapeutic effect, providing more options for the treatment of chronic pain.

## The Effect of Different Dosage Forms on Bioavailability and Efficacy (Figure 4)

The bioavailability of PEA is relatively low, which limits its clinical applications. In order to improve the bioavailability and efficacy of PEA, researchers have developed various formulations, such as conventional PEA, microparticulate PEA, ultramicroparticulate PEA, and nanopreparations.

Conventional PEA has a larger particle size, lower solubility, and slower absorption. Micronized PEA increases solubility and enhances absorption speed and bioavailability by reducing particle size. Ultrafine PEA has an even smaller particle size, which can better penetrate biological membranes, improving the drug's targeting and efficacy. Nanopreparations can encapsulate PEA in nanocarriers, protecting the drug from degradation, prolonging the release time, and improving the drug's bioavailability and efficacy.

Research by Tronino et al[55] indicates that lipid nanoparticles enhance the transdermal diffusion of N-Palmitoylethanolamide and prolong its anti-inflammatory and analgesic effects in vivo. Lipid nanoparticles appear to be a promising nanotechnology-based strategy for delivering N-Palmitoylethanolamide to clinical settings.

Impellizzeri et al[56] found that in an inflammatory pain rat model, micronized/submicronized PEA showed superior oral efficacy compared to non-micronized PEA.

Evangelista et al[57] conducted an open-label randomized controlled trial aimed at assessing the efficacy of ultra-fine powdered PEA in reducing pain intensity and improving sleep quality in patients with neuropathic pain due to carpal tunnel syndrome. The results indicated that by the end of the preoperative period, the overall sleep quality in the treatment group was significantly improved, with increased sleep duration, reduced sleep latency, and disturbances, as well as significant relief of pain symptoms.

These studies indicate that different formulations of PEA vary in bioavailability and efficacy. Choosing the appropriate formulation can enhance the clinical efficacy of PEA. For instance, for pain that requires a rapid onset of action, ultramicronized PEA can be selected; for pain that requires long-term maintenance of efficacy, nanoparticle formulations can be chosen.

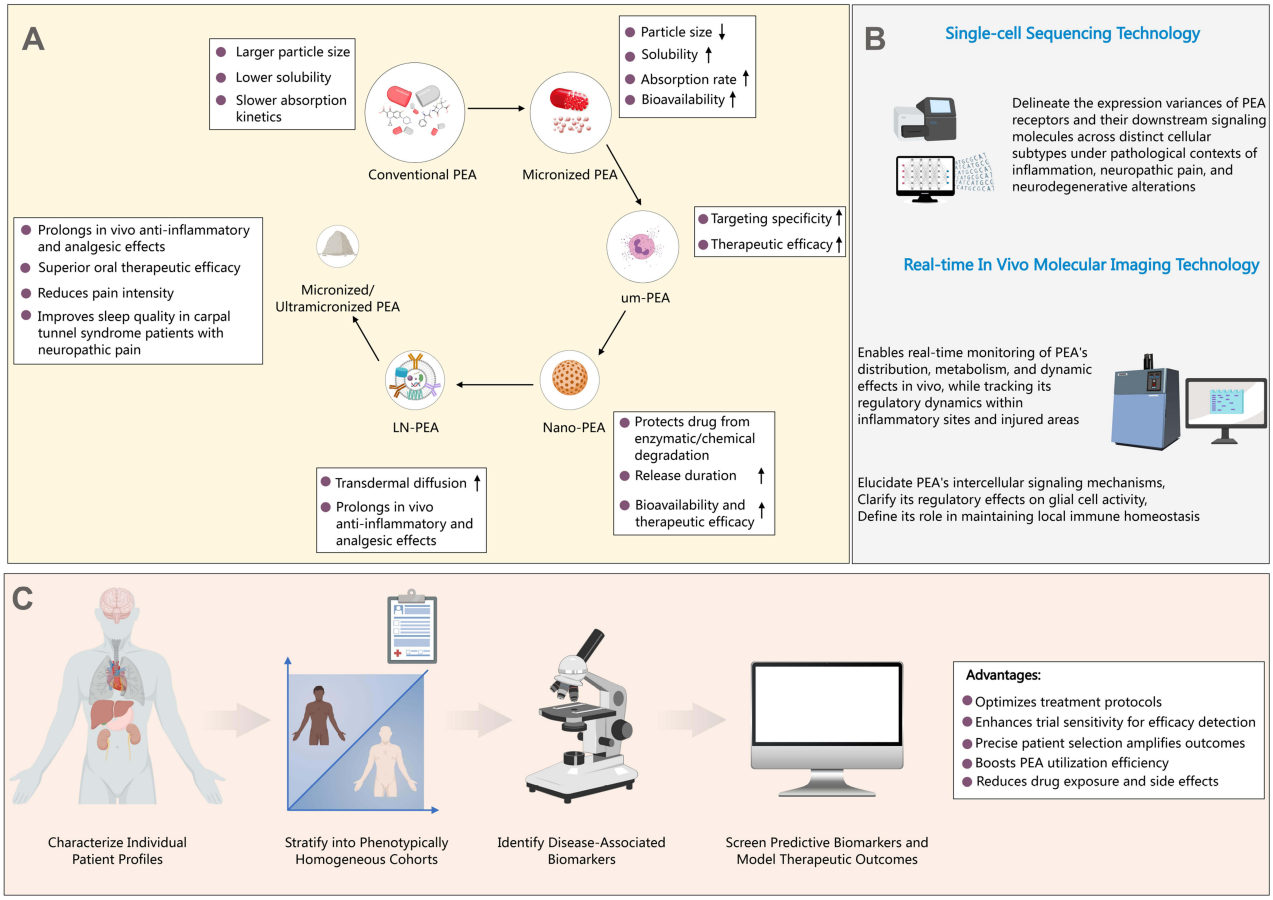


**Figure 4** The formulation improvement and precision medical application of PEA. (**A**) The different drug formats of PEA. (**B**) The methods to delineate the expression variances of PEA receptors and downstream molecules including single cell sequencing technology and real-time molecular imaging technology. (**C**) The advantages of PEA in clinic.

# Clinical Trial Data and Evidence-Based Analysis

## Summary of Various Randomized Controlled Trials and Observational Study Data

The clinical studies included in the analysis mainly consist of randomized controlled trials (RCTs) and observational studies, with selection criteria generally including study design, sample size, and clearly defined types of pain. PEA has been widely used in the management of different types of pain, including neuropathic pain and chronic inflammatory pain (Table 1).

### Pain Score and Functional Indicators

Commonly used assessment tools include the Visual Analog Scale (VAS), the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), among others. These tools are clinically significant as they can quantify the severity of patients' pain and functional impairment.[45,58]

The key research findings are summarized as follows:

### The Improvement in Pain Scores with PEA Monotherapy

Numerous studies have shown that PEA monotherapy can significantly reduce pain scores. For example, one study indicated that oral PEA treatment is associated with reduced skin adverse reactions related to interferon-β1a in patients with multiple sclerosis, resulting in improved pain perception.[16] Another study demonstrated that ultramicronized PEA can significantly alleviate pain intensity and neuropathic pain components in patients with chronic low back pain.[59]

A meta-analysis of aggregated data on chronic pain showed that PEA can reduce pain intensity by 1.04 points every two weeks.[19,47]

### Changes in Functional Indicators

PEA not only relieves pain but also improves patients' physical activity and sleep quality. Research shows that the WOMAC functional scores in the PEA group significantly improved, indicating that PEA can effectively enhance patients' quality of life.[45] In patients with carpal tunnel syndrome, treatment with ultrafine PEA can improve sleep quality, prolong continuous sleep duration, and reduce sleep latency and sleep disorders.[57]

### Differences in Efficacy at Different Doses or Treatment Durations

Regarding the dose effect of PEA, studies indicate that higher doses (such as 600 mg/day) may be more effective than lower doses (such as 300 mg/day), but the specific dosage should be adjusted according to the individual patient's condition.[60] Some studies have also examined the differences in efficacy of various treatment durations; for instance, a 12-week trial showed that the combined use of PEA and alpha-lipoic acid can effectively treat chronic prostatitis/chronic pelvic pain syndrome.[58] The benefits of long-term use of PEA have also been observed in other studies, such as in osteoarthritis pain models, where PEA was able to reduce inflammation and pain.[43]

## Chart Presentation and Interpretation

In clinical trials, forest plots, curves, and Kaplan–Meier curves are widely used to present and interpret data. The selection of these charts is based on their ability to effectively display the effect sizes and pain relief times of different studies.

### Forest Plot

Forest plots are commonly used to display the effect sizes and confidence intervals of different studies, helping to assess the consistency of PEA treatment effects. For example, a certain forest plot shows that the standardized mean difference (SMD) for the PEA group compared to the placebo is −1.2 (95% CI: −1.5 to −0.9), indicating that PEA has a significant analgesic effect.[47]

### Curve Chart

The curve chart can intuitively show the onset time and duration of effect of PEA. For example, the curve chart shows that patients experience significant pain improvement two weeks after using PEA, and the effect persists. In some studies, Kaplan–Meier curves were used to assess the duration of pain relief and compare the effectiveness of different treatment regimens.[47]

### Kaplan–Meier Curve

The Kaplan–Meier curve can show the duration of pain relief. For example, in one study, the Kaplan–Meier curve indicated that 81% of patients receiving PEA treatment had a pain score of 3 or lower after 60 days of treatment, compared to only 40.9% in the control group.[47]

# Safety and Tolerance Analysis

## Comparison of Adverse Reactions

PEA generally has good safety and tolerance, with a low incidence of adverse reactions. Common adverse reactions include gastrointestinal discomfort and dizziness, but they are usually mild and occur at a far lower rate than the risk of gastrointestinal bleeding that traditional analgesics like NSAIDs may cause. Compared to opioids, PEA does not have notable side effects such as constipation and motor coordination disorders.[59,61]

Some studies have assessed the tolerability of different populations. For example, in elderly patients, PEA has shown good tolerability, making it an attractive option for the management of chronic pain.[60,62] In terms of dose-dependent responses, although high doses of PEA may increase the risk of adverse effects in some individuals, overall, the safe dosage range for PEA is broader, with significant individual variability.[16]

### Data Heterogeneity and Bias

When analyzing clinical trial data, it is important to pay attention to potential sources of bias that may affect the results, such as study design, patient baseline differences, and so on. Data heterogeneity may arise from differences in patient populations across studies, variations in types of pain, and differences in formulations of PEA.[58]

To reduce heterogeneity, subgroup analyses can be conducted, such as stratifying by pain type to separately assess the effects of PEA on neuropathic and inflammatory pain. Additionally, tools like the Cochrane risk of bias assessment tool can be used to evaluate study quality and identify potential bias risks.[35]

In terms of data integration, it is important to avoid simply listing research results; instead, one should compare the consistency of conclusions across different studies through tables or textual analysis and conduct critical analysis. It should point out the limitations of current data, such as insufficient sample size and short follow-up duration, and provide direction for future research. For instance, although most RCTs support the analgesic effect of PEA, the negative results of a certain study may be related to the higher baseline pain severity of patients, suggesting the need to optimize inclusion criteria for specific subgroups in future studies. For example, one study included 73 patients with neuropathic pain caused by spinal cord injury, and the results showed no difference in pain intensity reduction between PEA-um and placebo. However, the study also emphasized that PEA did not cause more side effects than placebo, indicating that PEA has good safety.[35]

In terms of clinical translation, explaining the differences in efficacy by combining the mechanism of action of PEA (such as PPAR-α activation) enhances logical coherence. For example, PEA exerts anti-inflammatory and analgesic effects by activating PPAR-α receptors, which may explain why PEA's efficacy is more significant in certain inflammatory pain models.[26] At the same time, PEA's influence on the endogenous cannabinoid system may also play a role in the alleviation of neuropathic pain.[31]

Overall, clinical trial data and evidence-based analysis indicate that PEA has potential therapeutic value in various types of pain, especially in the management of chronic pain and neuropathic pain. Its good safety and tolerability make it an ideal alternative or adjunct to traditional analgesics. However, future research should still focus on dose optimization, individualized responses, and the impact of different formulations on efficacy to further enhance the clinical application value of PEA.

## Mechanism Research and Future Outlook

This chapter mainly discusses the emerging technological applications in the research of the mechanism of PEA in recent years, personalized precision medical strategies, and the future directions of interdisciplinary integration and combined therapy. With the continuous development in the fields of molecular biology, neuroscience, and clinical pharmacology, new technologies and multidisciplinary approaches are providing fresh perspectives and solid evidence to reveal the deeper mechanisms of PEA in anti-inflammatory, analgesic, and neuroprotective effects, while also pointing the way to optimizing clinical medication plans and formulating personalized treatment strategies (Figure 4).

### Application Prospects of New Technologies in the Study of PEA Mechanism of Action

#### Single-Cell Sequencing, Real-Time in vivo Molecular Imaging, and Multimodal Neuroimaging

In recent years, the rapid development of single-cell sequencing technology (Single-Cell RNA Sequencing) has enabled researchers to analyze complex gene expression profiles in the nervous system and immune cells at the single-cell level (Figure 4B). By utilizing this technology, scientists hope to distinguish the expression differences of PEA receptors (such as PPAR-α) and their downstream signaling molecules among different cell subtypes in the context of inflammation, neuropathic pain, and neurodegenerative changes, thereby constructing a more detailed map of cellular regulatory networks. By deeply analyzing the activity of PEA-responsive signaling pathways in different cell populations, not only can the specific mechanisms of PEA in inhibiting key inflammatory signaling pathways such as NF-κB and p38-MAPK be elucidated, but also new targets that have not yet been fully recognized can be discovered, which is of great significance for subsequent drug design and functional validation.[26–29]

Meanwhile, the development of real-time live molecular imaging technology has provided unprecedented possibilities for observing the distribution, metabolism, and dynamic effects of PEA in vivo. By utilizing fluorescently labeled probes,

near-infrared imaging, and bioluminescent systems, information on the spatiotemporal distribution of PEA in the central and peripheral nervous systems can be directly obtained from live animal models. This technology allows for real-time monitoring of the dynamic regulation process of PEA at inflammation sites and injury areas after administration, providing direct evidence for revealing how PEA transmits signals between cells, regulates glial cell activity, and maintains local immune homeostasis. Additionally, multimodal neuroimaging (such as functional magnetic resonance imaging, positron emission tomography, and diffusion tensor imaging) offers strong data support for assessing the impact of PEA on brain functional networks from a macroscopic perspective. By combining the specific effects at the molecular level with changes in the neural network at the systemic level, a panoramic view of PEA's effects from micro to macro can be constructed, providing a comprehensive perspective for understanding its role in alleviating chronic pain and cognitive dysfunction.

Based on the application of these advanced technologies, future research is expected to achieve breakthroughs in several areas: first, revealing changes in signaling pathways within various cell types regulated by PEA through single-cell sequencing, which will help uncover the sensitivity and response differences of different subtype cells to PEA; second, real-time in vivo molecular imaging technology will be able to reveal the specific dynamic changes of PEA in inflammation and nerve injury areas, assisting researchers in precisely locating the action areas and targeted cells of PEA through the dual information of spatial positioning and temporal resolution; third, the integration of multimodal neuroimaging data can transform molecular biology findings into explanations of their impact on overall nervous system function, thereby better assessing the potential applications of PEA in clinically improving neural functions and alleviating pain (Figure 4B).

### Explore the Precise Mechanism of PEA in Neural Repair and Synaptic Remodeling

In the context of chronic pain and neuropathic pain, the damage, repair, and plastic changes of nerve cells directly affect patients' pain experiences and cognitive functions. Numerous experimental studies have shown that PEA not only exerts anti-inflammatory and analgesic effects but may also promote the restoration of the structure and function of the nervous system by regulating neuro-regeneration and synaptic remodeling processes. For example, in nerve injury models, it has been observed that PEA can inhibit the sustained release of inflammatory mediators by activating the PPAR-α signaling pathway, thereby providing a more favorable microenvironment for the regeneration of nerve cells. At the same time, PEA can also regulate the phosphorylation state of AMPA receptor subunits and the expression of postsynaptic density proteins, promoting the reconstruction of synaptic structures and increasing the efficiency of neurotransmission.[24] These effects not only help repair damaged neural circuits but may also improve memory impairments and cognitive decline caused by nerve injuries.

Further research can utilize electrophysiological recording techniques, two-photon microscopy, and optogenetic tools to monitor the role of PEA in neurons and glial cells in real time. These techniques can quantitatively analyze neuronal firing patterns, synaptic transmission, and long-term potentiation (LTP) changes, thereby allowing for a more precise assessment of PEA's role in regulating intracellular signaling processes. Meanwhile, studies based on gene knockout and transgenic animal models can also help clarify the relative contributions of PPAR-α and other potential targets in PEA-mediated nerve repair. The current preliminary research results provide strong support for PEA in neural repair and synaptic plasticity remodeling, but its optimal intervention timing, dose dependence, and interactions with other regulatory factors still need further exploration, laying the theoretical foundation for developing precise treatment plans in the future.

## New Strategies for Personalized and Precision Medicine

### Patient Stratification Management and the Application of Biomarkers in PEA Treatment

In clinical practice, different patients exhibit significant heterogeneity in their responses to PEA treatment due to variations in genetic background, disease progression stage, and inflammatory responses. To achieve precision therapy, patient stratification management has become an important strategy, which focuses on dividing patients into subgroups with similar molecular phenotypes and clinical presentations based on individual characteristics, while exploring biomarkers closely related to the efficacy of PEA. Through high-throughput genomics, proteomics, and metabolomics

analysis, researchers can identify a series of candidate biomarkers, such as indicators associated with PPAR-α receptor activity, levels of inflammatory mediators, and neurotrophic factors (like BDNF), which are expected to predict patients' sensitivity and response level to PEA treatment.

The hierarchical management strategy not only helps to optimize treatment plans but also significantly improves the efficacy detection capacity of clinical trials. When designing trials, considering patients' genetic polymorphisms, disease duration, and inflammatory levels can more precisely define trial inclusion criteria, making the treatment effects more evident. Future research needs to validate the predictive efficacy of these biomarkers in large patient cohorts and establish a patient stratification system based on multivariable models to provide evidence-based support for the clinical implementation of personalized treatment. This classification management based on individual patient characteristics not only aids in enhancing the utilization efficiency of PEA but also reduces unnecessary drug exposure and the risk of side effects.

### Use N-of-1 Trials or Multicenter Large-Sample Studies to Determine the Optimal Dosage and Administration Method

Given the significant differences in efficacy and tolerability of PEA treatment among different individuals, determining its optimal dosage and administration scheme has become an urgent problem to be solved. N-of-1 trials, as a cross-over controlled design method focusing on a single patient, are gradually gaining attention. By alternately using PEA and a placebo in the same patient and continuously recording efficacy indicators (such as pain scores, functional improvements, etc), it is possible to eliminate the interference caused by inter-group differences, providing precise data for individualized administration. Such trials are particularly suitable for patient populations with complex clinical presentations and uncertain results from traditional large sample randomized controlled trials, achieving the goal of precision medicine while ensuring scientific rigor.

Corresponding to N-of-1 trials, multi-center large-sample randomized controlled trials can statistically derive the overall dose-response curve and pharmacokinetic characteristics of PEA at the population level. By collaborating across centers and gathering data from patients of different regions and backgrounds, the statistical power of the trials can be significantly enhanced, thereby more accurately capturing the optimal time window, dose range, and administration routes for PEA. In the future, combining the advantages of these two research methods within a design model that is both broadly applicable and considerate of individual differences will undoubtedly establish a scientific and systematic standardized approach for the precise clinical application of PEA (Figure 4C).

## Future Directions of Interdisciplinary Integration and Collaborative Therapy

### The Synergy of Molecular Biology, Neuroimaging, and Clinical Pharmacology

In contemporary medical research, complex diseases such as chronic pain, neuropathic pain, and neurodegenerative diseases often involve multiple mechanisms, multiple signaling pathways, and the synergistic dysregulation of various cell types. A single discipline struggles to comprehensively reveal the pathophysiological processes of these diseases, while multidisciplinary collaboration and integration can overcome this limitation. Molecular biology provides direct evidence for unveiling the microscopic mechanisms of PEA in cellular signaling, gene regulation, and inflammatory intervention; neuroimaging utilizes technologies such as fMRI, PET, and DTI to visually demonstrate the effects of PEA on brain functional networks, neural circuit connectivity, and pathological structural changes; and clinical pharmacology focuses on analyzing the pharmacokinetics, drug metabolism, dosage effects, and safety issues of PEA, which in turn guides practical application.

This multidimensional integration of molecules, imaging, and clinical research not only aids in systematically explaining the mechanism of action of PEA from different levels but also facilitates a seamless connection from basic research to clinical application. For example, after revealing the key targets of PEA in regulating inflammation and neuroprotection through molecular biological methods, real-time monitoring of the distribution and changes of these targets in the central nervous system can be carried out using neuroimaging, and further combined with clinical pharmacological data for dosage optimization and efficacy prediction, forming a closed-loop feedback system. In this

way, both basic theoretical research can be advanced, and better service can be provided for clinical treatment, ultimately achieving the dual goals of pain management and neurofunctional recovery (Figure 4).

Preliminary data that currently exists suggest that changes in PEA-regulated signaling pathways at the molecular level can manifest as functional recovery in specific brain regions on imaging, while clinical pharmacology data show that appropriate doses of PEA can maximize its neuroprotective and analgesic effects. Establishing interdisciplinary communication platforms and data-sharing mechanisms in the future will significantly accelerate in-depth research into this synergistic mechanism and promote the application of comprehensive analysis methods based on multidimensional data in clinical decision-making.

### Strategy for the Combined Application of Novel Small Molecule Intervention and PEA

Although PEA, as a pure natural lipid mediator, has significant anti-inflammatory, analgesic, and neuroprotective effects, single drug therapy often fails to meet the needs of all patients in the complex pathological processes of chronic pain and neuropathic pain. Recently, the development of new small molecule drugs has provided a broad prospect for combination therapy strategies. Unlike traditional single treatment methods, the combined application of PEA with other small molecule drugs that have complementary mechanisms is expected to enhance therapeutic effects while reducing the dosage of the single drug, thereby minimizing the risk of potential adverse reactions.

Certain small molecules that can modulate the activity of the endogenous cannabinoid system, or molecules that enhance antioxidant and anti-inflammatory functions, may exhibit synergistic effects when working in conjunction with PEA. Studies have shown that in animal experiments, the combined use of low doses of opioids or NSAIDs with PEA can significantly enhance analgesic effects without significantly increasing side effects.[20] Furthermore, new small molecule intervention methods also include candidate drugs capable of precisely targeting lesions or regulating the function of specific ion channels, which may complement PEA in their action targets and signaling pathways, promoting nerve repair, enhancing synaptic transmission, and improving intracellular homeostasis.

The exploration of combined therapeutic strategies requires multi-layered and multi-angle experimental validation. On one hand, in in vivo and in vitro models, it is necessary to first confirm whether the interactions between different drugs show synergistic or additive effects; on the other hand, through comprehensive assessments of drug metabolism, pharmacokinetics, and pharmacodynamics, the optimal combination ratios, timing of administration, and therapeutic windows between the components must be clarified. Modern pharmacological methods, such as dose-response curves, equivalence trials, and systems biology analytical tools, provide technical support for this process. Future research should integrate chemical synthesis, cell biology, animal model experiments, and preclinical evaluation data to construct a multi-parameter combined evaluation system, thereby providing scientific guidance for the combined application strategies of PEA and novel small molecule interventions.

Collectively, through the gradual application of new technologies, continuous optimization of individual stratification and precision medical strategies, and ongoing exploration of interdisciplinary integration and combined treatment models, the future role and clinical application of PEA in the treatment of chronic pain and neuropathic pain will likely see significant breakthroughs. This series of innovative measures will not only help reveal the intrinsic mechanisms of PEA's multi-target and comprehensive regulation but also promote the development of more scientific and personalized treatment plans, providing patients with safer and more effective new options for pain management.

## Conclusions and Prospects

### Comprehensive Summary of the Multiple Mechanisms of PEA in Pain, Inflammation Regulation, and Neuroprotection

A large number of foundational experiments and animal model studies have shown that PEA, as an endogenous lipid mediator, plays a unique and extensive role in pain relief, inflammation control, and neuroprotection. It can effectively regulate pain and its related inflammatory responses through the synergistic action of multiple molecular signaling pathways. One of its main mechanisms is to regulate downstream signaling pathways by activating PPAR-α, thereby inhibiting the activity of NF-κB to reduce the expression of pro-inflammatory cytokines (such as tumor necrosis factor-

alpha, interferon-gamma, and interleukin-17).[16] This mechanism not only helps to attenuate local inflammatory responses but also reduces pain sensitivity caused by excessive neuronal activation.

On the other hand, PEA has a companion effect with the endogenous cannabinoid system; although it does not directly activate CB1 or CB2 receptors itself, it can enhance the effects of endogenous cannabinoids such as AEA, thereby indirectly regulating neurotransmission and pain modulation. Additionally, PEA can reduce the release of inflammatory mediators within the nervous system by regulating the activity of glial cells, particularly microglia and astrocytes, thereby protecting the central nervous system from inflammatory damage. This regulatory mechanism has been validated in many neuropathic pain models, capable of improving synaptic plasticity in neurons, restoring LTP, and enhancing related cognitive functions.[25,40]

It is worth noting that PEA also has significant protective effects on the peripheral nervous system. In animal models of chronic pain and neuropathic pain, PEA can significantly reduce oxidative stress responses triggered by nerve injury and improve the regeneration and repair of damaged nerves. This process involves not only the inhibition of downstream inflammatory signals (such as the p38-MAPK pathway) but also the regulation of ion channel functions and neurotrophic factors (such as BDNF), enabling neurons to recover normal functions more quickly after external injury.[25]

Besides, PEA can also regulate immune cells, particularly its stabilizing effect on mast cells plays a crucial role in inflammatory pain. By reducing the degranulation of mast cells and the release of related inflammatory mediators (such as nerve growth factor and vascular endothelial growth factor), PEA has shown significant anti-inflammatory and analgesic effects in various inflammatory diseases (such as visceral pain induced by the endometriosis model with urinary stones).[63] The synergistic action of multiple targets in this mechanism not only provides a theoretical basis for the application of PEA in acute inflammation and chronic pain but also lays the foundation for its expanded application in nerve repair and disease prevention.

Generally, the multiple mechanisms of PEA are reflected in several aspects: Firstly, through the activation of PPAR-α, it inhibits key signaling pathways such as NF-κB and p38-MAPK, reducing the generation of pro-inflammatory factors at the source; Secondly, by acting as a partner of the endocannabinoid system, PEA enhances the endogenous analgesic mechanism; thirdly, PEA reduces local and central inflammation by regulating the activity of glial cells and mast cells, thereby protecting neurons and promoting the recovery of neural plasticity.[16,25,26] The interplay of these mechanisms gives PEA a significant advantage in improving pain, controlling inflammation, and protecting nerve cells, providing a scientific basis for the future development of novel analgesic and neuroprotective drugs.

## The Unique Advantages and Challenges of PEA in Clinical Applications

Based on numerous clinical studies and practical application cases, PEA has shown relatively high safety and good tolerance in the treatment of various pain diseases, giving it a clear advantage over traditional analgesics such as opioids and non-steroidal anti-inflammatory drugs (Figure 4C). In some clinical trials involving neuropathic pain, chronic low back pain, and pelvic pain, oral ultra-micronized PEA as an adjunct therapy not only effectively reduced patients' dependence on conventional analgesics but also significantly improved pain scores and quality of life.[37,59,60]

PEA, as an endogenous lipid that naturally exists in food and the body, has low toxicity, good tolerance, and lacks obvious drug-drug interactions, which is particularly important in complex pathological conditions (such as elderly patients with polypharmacy). For example, the N-of-1 trial method was used to verify the positive effects of PEA in chronic pain management among elderly patients, not only improving pain symptoms but also enhancing functional status and quality of daily life, providing clinicians with a personalized precision treatment plan.[60,62]

Despite the unique pharmacological advantages of PEA, there are still challenges in its clinical promotion. First, there are certain differences in the dosage forms of PEA used in different clinical trials (such as conventional, microparticulated, ultramicronized, or nanomedicine), which have a direct impact on bioavailability and efficacy.[55] Studies have shown that ultramicronized PEA has higher in vivo distribution efficiency and more lasting analgesic effects. Therefore, how to standardize products through appropriate formulation processes has become an urgent issue that needs to be addressed (Figure 4A). Secondly, although several clinical studies have shown that PEA has positive effects on various pain conditions, some studies have limitations such as short follow-up durations and small sample sizes, which pose challenges to the stability and generalizability of the results. In clinical trials for neuropathic pain after spinal cord injury,

while some studies failed to observe significant differences compared to the placebo group, overall adverse events were very few, indicating that its safety advantages remain evident.[35] Furthermore, differences among patients, such as genetic background, previous medication history, levels of inflammation, and the complexity of pain types, may all influence the therapeutic effects of PEA, necessitating further exploration of individualized treatment strategies and dose optimization in future clinical research.

While the combined application of PEA with other drugs (such as opioids, NSAIDs, alpha-lipoic acid, and other natural antioxidants) has shown synergistic analgesic effects, the optimal combination ratios between different drugs, the mechanisms of interaction, and long-term safety still require more evidence-based research for validation.[20,58,61] Overall, PEA demonstrates unique and multiple advantages in clinical applications, but it is inevitably restricted by factors such as formulation standards, dosage optimization, patient heterogeneity, and combination medication strategies, all of which point to directions for improvement in future clinical translational research.

## A Call for Large-Scale and Precise Clinical Trials and Interdisciplinary Collaboration in Future

Future research should build on the existing foundation and conduct large-scale, multi-center, randomized controlled trials to comprehensively verify the efficacy and safety of PEA in various types of pain and neurodegenerative diseases using objective and rigorous evidence-based medical methods. From preliminary mechanistic studies to clinical applications, there is an urgent need to establish a standardized dosage and administration scheme to clarify the optimal application strategies of different formulation products under various pathological conditions. This will not only help improve therapeutic outcomes but also reduce the variability in efficacy and interindividual differences caused by different formulation processes.

To achieve this goal, future research needs to closely integrate cutting-edge innovations from multiple disciplines, including molecular biology, neuroimaging, clinical pharmacology, and medicinal chemistry. For example, using single-cell RNA sequencing technology, detailed molecular characterization of pain-related cell populations can be conducted, thereby deepening the understanding of PEA's regulatory effects on glial cells and immune cells; real-time in vivo molecular imaging technology and multimodal neuroimaging will also provide reliable data for observing the effects of PEA on synaptic plasticity and neural network remodeling in the brain and spinal cord.[25,40]

Additionally, future research should emphasize interdisciplinary collaboration, integrating data from basic research and clinical trials to create a comprehensive evaluation system that ranges from molecules and cells to organs and overall functions. For instance, the N-of-1 trial method used in some recent randomized controlled trials not only allows for precise efficacy assessment tailored to individual patients but also provides insights for optimizing group treatment plans, making clinical decision-making more personalized and precise.[60,62]

In terms of combination therapy, exploring the synergistic mechanisms of PEA with other analgesics or anti-inflammatory drugs (such as opioids, gabapentin, natural antioxidants, and plant extracts) will provide possibilities for developing new multi-target combination therapy strategies. This not only helps achieve the desired analgesic effect while reducing the dosage and side effects of traditional drugs, but also promotes the shift from single-drug treatment to multimodal and multi-target therapies, effectively addressing chronic pain and neurodegenerative diseases caused by complex and multifaceted factors.[20,58,61]

Future clinical trials should further expand the sample size and follow-up duration, utilize rigorous randomized controlled designs to eliminate bias, while paying attention to individual differences, and achieve patient stratification management through means such as biomarkers. Only with a more detailed understanding of each patient's biological status and pain characteristics can the concept of precision medicine be truly implemented. In addition, multi-center cooperation among countries and regions will provide broader data support for the efficacy evaluation of PEA in different populations, thereby accelerating the clinical promotion of PEA worldwide.

Collectively, promoting the transition of PEA from basic science to clinical application requires efforts in the following areas: First, conducting large-scale, long-term, multi-center randomized controlled trials to systematically evaluate the efficacy and safety of PEA in different types of pain; Secondly, optimizing the dosage form and

preparation process of PEA to ensure sufficient bioavailability in the body; Third, utilizing new technologies to deeply analyze the multiple molecular mechanisms of PEA, particularly its fine roles in neuroprotection and synaptic remodeling; Fourth, strengthening interdisciplinary and international cooperation to integrate advantageous resources from different fields to jointly advance the development of personalized precision medicine.[47,55,64] With the in-depth clarification of multiple mechanisms, sufficient accumulation of clinical data, and the promotion of interdisciplinary collaborative innovation, PEA is expected to become a safe and effective innovative analgesic and neuroprotective drug with multiple target regulation in the future, opening new therapeutic prospects for patients with chronic pain and neurological diseases.

## Abbreviations

AEA, N-arachidonoylethanolamine; ALA, α-lipoic acid; ALC, Acetyl-L-Carnitine; BDNF, Brain-derived neurotrophic factor; CIPN, Chemotherapy-induced neuropathic pain; DLX, Duloxetine; DN, Diabetic neuropathy; DRG, Dorsal root ganglion; ECS, Endogenous cannabinoid system; FAAH, Fatty acid amide hydrolase; FASmod, Fibromyalgia Assessment Status; FIQR, Fibromyalgia Impact Questionnaire-Revised; HPA, Hypothalamic-pituitary-adrenal; IC/BPS, Interstitial cystitis/bladder pain syndrome; LTP, Long-term potentiation; m-PEA-Pol, Micronized-PEA-Polydatin; NAAA, N-acylethanolamine acid amidase; NAPE-PLD, N-acylphosphatidylethanolamine-specific phospholipase D; NF-κB, Nuclear factor kappa B; NGF, Nerve growth factor; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; NMDA, N-methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs; PEA, Palmitoylethanolamide; PEA-Q, PEA with the natural antioxidant quercetin; PEAum, Ultra-micronized palmitoylethanolamide; PGB, Pregabalin; PPAR-α, Proliferator-activated receptor alpha; RCTs, Randomized controlled trials; SMD, Standardized mean difference; SNI, Sciatic nerve injury; SOD, Superoxide dismutase; TH, Thalamic hemorrhage; umPEA, ultra-micronized PEA; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WPI, Widespread Pain Index.

## Data Sharing Statement

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

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## Author Contributions

All authors contributed significantly to the work reported, including conception, theme design, literature search and screening, acquisition of data, analysis and interpretation, graphics production, drafting, reviewing, and revising of articles. All authors have participated in the submission of the article to the journal and agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript to be published and have agreed to be accountable for all aspects of the work.

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## References


1. Kissoon NR. Chronic widespread pain. *Continuum*. 2024;30(5):1427–1446. doi:10.1212/CON.0000000000001470
2. Wang V, Bačkonja M. Peripheral neuropathic pain. *Continuum*. 2024;30(5):1363–1380. doi:10.1212/CON.0000000000001474
3. Glare P, Mahendran M, Weiss AD. Update on chronic pain management. *Intern Med J*. 2025;55(2):200–206. doi:10.1111/imj.16589
4. Ahmadi R, Kuner R, Weidner N, Keßler J, Bendszus M, Krieg SM. The diagnosis and treatment of neuropathic pain. *Dtsch Arztebl Int*. 2024;121 (25):825–832. doi:10.3238/arztebl.m2024.0215
5. Okine BN, Madasu MK, McGowan F, et al. N-palmitoylethanolamide in the anterior cingulate cortex attenuates inflammatory pain behaviour indirectly via a CB1 receptor-mediated mechanism. *Pain*. 2016;157(12):2687–2696. doi:10.1097/j.pain.0000000000000687
6. Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nat Neurosci*. 2007;10(11):1361–1368. doi:10.1038/nn1992
7. Anisimov ED, Andrushkevich OM, Dzhafarov VM, Amelina EV, Rzaev JA, Slavin KV. Long-term effects of spinal cord stimulation on pain in postherpetic neuralgia. *Stereotact Funct Neurosurg*. 2025;103(1):35–41. doi:10.1159/000542138
8. Zhang S, Ning Y, Yang Y, et al. Decoding pain chronification: mechanisms of the acute-to-chronic transition. *Front Mol Neurosci*. 2025;18:14.46367. doi:10.3389/fnmol.2025.1596367
9. Knezevic NN. Chronic stress and headaches: the role of the HPA axis and autonomic nervous system. *Biomedicines*. 2025;13(2):463. doi:10.3390/biomedicines13020463
10. Jiang YP, Wen JJ, Ma X, et al. CRMP2 phosphorylation regulates polarization and spinal infiltration of CD4+ T lymphocytes, inhibits spinal glial activation, and arthritic pain. *Pain*. 2025;10–97. doi:10.1097/j.pain.0000000000003599
11. Medoro A, Davinelli S, Fogacci F, et al. Palmitoylethanolamide in postmenopausal metabolic syndrome: current evidence and clinical perspectives. *Nutrients*. 2024;16(24):4313. doi:10.3390/nu16244313
12. Basu D. Palmitoylethanolamide, an endogenous fatty acid amide, and its pleiotropic health benefits: a narrative review. *J Biomed Res*. 2024;39 (3):215–228. doi:10.7555/JBR.38.20240053
13. Flannery LE, Kerr DM, Hughes EM, et al. N-acylethanolamine regulation of TLR3-induced hyperthermia and neuroinflammatory gene expression: a role for PPARα. *J Neuroimmunol*. 2021;358:577654. doi:10.1016/j.jneuroim.2021.577654
14. Mock ED, Gagestein B, van der Stelt M. Anandamide and other N-acylethanolamines: a class of signaling lipids with therapeutic opportunities. *Prog Lipid Res*. 2023;89:101194. doi:10.1016/j.plipres.2022.101194
15. D'Aloia A, Molteni L, Gullo F, et al. Palmitoylethanolamide modulation of microglia activation: characterization of mechanisms of action and implication for its neuroprotective effects. *Int J Mol Sci*. 2021;22(6):3054. doi:10.3390/ijms22063054
16. Orefice NS, Alhouayek M, Carotenuto A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. *Neurotherapeutics*. 2016;13(2):428–438. doi:10.1007/s13311-016-0420-z
17. Briskey D, Skinner R, Smith C, Rao A. Effectiveness of Palmitoylethanolamide (Levagen+) compared to a placebo for reducing pain, duration, and medication use during migraines in otherwise healthy participants-a double-blind randomised controlled study. *Pharmaceuticals*. 2024;17(2):145. doi:10.3390/ph17020145
18. Bartolucci ML, Marini I, Bortolotti F, et al. Micronized palmitoylethanolamide reduces joint pain and glial cell activation. *Inflamm Res*. 2018;67 (10):891–901. doi:10.1007/s00011-018-1179-y
19. Viña I, López-Moreno M. Meta-analysis of palmitoylethanolamide in pain management: addressing literature gaps and enhancing understanding. *Nutr Rev*. 2025;83(7):e1604–e1618. doi:10.1093/nutrit/nuae203
20. Déciga-Campos M, Jaramillo-Morales OA, Espinosa-Juárez JV, Aguilera-Martínez ME, Ventura-Martínez R, López-Muñoz FJ. N-palmitoylethanolamide synergizes the antinociception of morphine and gabapentin in the formalin test in mice. *J Pharm Pharmacol*. 2023;75 (9):1154–1162. doi:10.1093/jpp/rgad004
21. Santonocito S, Donzella M, Venezia P, Nicolosi G, Mauceri R, Isola G. Orofacial pain management: an overview of the potential benefits of palmitoylethanolamide and other natural agents. *Pharmaceutics*. 2023;15(4):1193. doi:10.3390/pharmaceutics15041193
22. Mulè S, Rosso G, Botta M, et al. Design of mixed medicinal plants, rich in polyphenols, vitamins B, and palmitoylethanolamide-based supplement to help reduce nerve pain: a preclinical study. *Int J Mol Sci*. 2024;25(9):4790. doi:10.3390/ijms25094790
23. Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. *Pain Ther*. 2015;4(2):169–178. doi:10.1007/s40122-015-0038-6
24. Varrassi G, Rekatsina M, Leoni MLG, et al. A decades-long journey of Palmitoylethanolamide (PEA) for chronic neuropathic pain management: a comprehensive narrative review. *Pain Ther*. 2025;14(1):81–101. doi:10.1007/s40122-024-00685-4
25. Boccella S, Cristiano C, Romano R, et al. Ultra-micronized palmitoylethanolamide rescues the cognitive decline-associated loss of neural plasticity in the neuropathic mouse entorhinal cortex-dentate gyrus pathway. *Neurobiol Dis*. 2019;121:106–119. doi:10.1016/j.nbd.2018.09.023
26. Zhou G, Fu X, Wang L, et al. Palmitoylethanolamide ameliorates neuroinflammation via modulating PPAR-α to promote the functional outcome after intracerebral hemorrhage. *Neurosci Lett*. 2022;781:136648. doi:10.1016/j.neulet.2022.136648
27. Siracusa R, Fusco R, Cordaro M, et al. The protective effects of pre- and post-administration of micronized palmitoylethanolamide formulation on postoperative pain in rats. *Int J Mol Sci*. 2020;21(20):7700. doi:10.3390/ijms21207700
28. Argueta DA, Avalos B, Goel Y, et al. Neuroprotective, anti-inflammatory, and analgesic activity of palmitoylethanolamide in sickle cell mice. *Blood Adv*. 2025;9(12):3056–3068. doi:10.1182/bloodadvances.2024015439
29. Impellizzeri D, Peritore AF, Cordaro M, et al. The neuroprotective effects of micronized PEA (PEA-m) formulation on diabetic peripheral neuropathy in mice. *FASEB J*. 2019;33(10):11364–11380. doi:10.1096/fj.201900538R
30. Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. *Am J Hosp Palliat Care*. 2019;36(12):1134–1154. doi:10.1177/1049909119850807
31. Greco R, Demartini C, Zanaboni AM, et al. The endocannabinoid system and related lipids as potential targets for the treatment of migraine-related pain. *Headache*. 2022;62(3):227–240. doi:10.1111/head.14267
32. Morgia G, Lo Giudice A, Carrino M, et al. Efficacy of Palmitoylethanolamide, Epilobium and Calendula suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III. *Arch Ital Urol Androl*. 2024;96(2):12582. doi:10.4081/aiua.2024.12582

33. Clayton P, Subah S, Venkatesh R, Hill M, Bogoda N. Palmitoylethanolamide: a potential alternative to cannabidiol. *J Diet Suppl*. 2023;20(3):505–530. doi:10.1080/19390211.2021.2005733
34. Mabou Tagne A, Fotio Y, Lin L, et al. Palmitoylethanolamide and hemp oil extract exert synergistic anti-nociceptive effects in mouse models of acute and chronic pain. *Pharmacol Res*. 2021;167:105545. doi:10.1016/j.phrs.2021.105545
35. Andresen SR, Bing J, Hansen RM, et al. Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: a randomized, double-blind, placebo-controlled trial. *Pain*. 2016;157(9):2097–2103. doi:10.1097/j.pain.0000000000000623
36. Dai CQ, Guo Y, Chu XY. Neuropathic pain: the dysfunction of Drp1, Mitochondria, and ROS homeostasis. *Neurotox Res*. 2020;38(3):553–563. doi:10.1007/s12640-020-00257-2
37. Xu R, Pan Y, Zheng K, et al. IL-33/ST2 induces macrophage-dependent ROS production and TRPA1 activation that mediate pain-like responses by skin incision in mice. *Theranostics*. 2024;14(13):5281–5302. doi:10.7150/thno.97856
38. Zhang H, Xiang D, Liu X, Xiang L. PPARα agonist relieves spinal cord injury in rats by activating Nrf2/HO-1 via the Raf-1/MEK/ERK pathway. *Aging*. 2021;13(22):24640–24654. doi:10.18632/aging.203699
39. Polati E, Martini A, Schweiger V. Ultramicronized palmitoylethanolamide treatment in central neuropathic pain following longstanding spinal cord injury: try to extinguish the fire after everything was burned. *Pain*. 2017;158(4):763–764. doi:10.1097/j.pain.0000000000000821
40. Boccella S, Marabese I, Iannotta M, et al. Metabotropic glutamate receptor 5 and 8 modulate the ameliorative effect of ultramicronized palmitoylethanolamide on cognitive decline associated with neuropathic pain. *Int J Mol Sci*. 2019;20(7):1757. doi:10.3390/ijms20071757
41. Landolfo E, Cutuli D, Petrosini L, Caltagirone C. Effects of palmitoylethanolamide on neurodegenerative diseases: a review from rodents to humans. *Biomolecules*. 2022;12(5):667. doi:10.3390/biom12050667
42. Larauche M, Mulak A, Ha C, et al. FAAH inhibitor URB597 shows anti-hyperalgesic action and increases brain and intestinal tissues fatty acid amides in a model of CRF1 agonist mediated visceral hypersensitivity in male rats. *Neurogastroenterol Motil*. 2024;36(12):e14927. doi:10.1111/nmo.14927
43. Britti D, Crupi R, Impellizzeri D, et al. A novel composite formulation of palmitoylethanolamide and quercetin decreases inflammation and relieves pain in inflammatory and osteoarthritic pain models. *BMC Vet Res*. 2017;13(1):229. doi:10.1186/s12917-017-1151-z
44. Salaffi F, Farah S, Sarzi-Puttini P, Di Carlo M. Palmitoylethanolamide and acetyl-L-carnitine act synergistically with duloxetine and pregabalin in fibromyalgia: results of a randomised controlled study. *Clin Exp Rheumatol*. 2023;41(6):1323–1331. doi:10.55563/clinexprheumatol/pmdzcq
45. Scaturro D, Asaro C, Lauricella L, Tomasello S, Varrassi G, Letizia Mauro G. Combination of rehabilitative therapy with ultramicronized palmitoylethanolamide for chronic low back pain: an observational study. *Pain Ther*. 2020;9(1):319–326. doi:10.1007/s40122-019-00140-9
46. Elfarnawany A, Dehghani F. Palmitoylethanolamide mitigates paclitaxel toxicity in primary dorsal root ganglion neurons. *Biomolecules*. 2022;12(12):1873. doi:10.3390/biom12121873
47. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. *Pain Physician*. 2016;19(2):11–24.
48. Bonetti M, Lauritano D, Ottaviani GM, et al. Oxygen-ozone therapy associated with alpha lipoic acid plus palmitoylethanolamide and myrrh versus ozone therapy in the combined treatment of sciatic pain due to herniated discs: observational study on 318 patients. *Int J Environ Res Public Health*. 2022;19(9):5716. doi:10.3390/ijerph19095716
49. Tafuri A, Panunzio A, De Mitri R, Benetti F, Gaio E, Pagliarulo V. Micronized palmitoylethanolamide, hempseed oil, and maritime pine bark dry extract (Pelvipea®) for pelvic pain: an in vitro study for urothelial inflammation treatment. *Cells*. 2023;12(4):616. doi:10.3390/cells12040616
50. Cervigni M, Nasta L, Schievano C, Lampropoulou N, Ostardo E. Micronized palmitoylethanolamide-polydatin reduces the painful symptomatology in patients with interstitial cystitis/bladder pain syndrome. *Biomed Res Int*. 2019;2019:9828397. doi:10.1155/2019/9828397
51. Peritore AF, Siracusa R, Fusco R, et al. Ultramicronized palmitoylethanolamide and paracetamol, a new association to relieve hyperalgesia and pain in a sciatic nerve injury model in rat. *Int J Mol Sci*. 2020;21(10):3509. doi:10.3390/ijms21103509
52. Nobili S, Micheli L, Lucarini E, Toti A, Ghelardini C, Di Cesare Mannelli L. Ultramicronized N-palmitoylethanolamine associated with analgesics: effects against persistent pain. *Pharmacol Ther*. 2024;258:108649. doi:10.1016/j.pharmthera.2024.108649
53. Didangelos T, Karlafti E, Kotzakioulafi E, et al. Efficacy and safety of the combination of palmitoylethanolamide, superoxide dismutase, alpha lipoic acid, vitamins B12, B1, B6, E, Mg, Zn and Nicotinamide for 6 months in people with diabetic neuropathy. *Nutrients*. 2024;16(18):3045. doi:10.3390/nu16183045
54. Infantino R, Schiano C, Luongo L, et al. MED1/BDNF/TrkB pathway is involved in thalamic hemorrhage-induced pain and depression by regulating microglia. *Neurobiol Dis*. 2022;164:105611. doi:10.1016/j.nbd.2022.105611
55. Tronino D, Offerta A, Ostacolo C, et al. Nanoparticles prolong N-palmitoylethanolamide anti-inflammatory and analgesic effects in vivo. *Colloids Surf B Biointerfaces*. 2016;141:311–317. doi:10.1016/j.colsurfb.2016.01.058
56. Impellizzeri D, Bruschetta G, Cordaro M, et al. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. *J Neuroinflammation*. 2014;11:136. doi:10.1186/s12974-014-0136-0
57. Evangelista M, Cilli, De Vitis R, Militerno A, Fanfani F. Ultra-micronized palmitoylethanolamide effects on sleep-wake rhythm and neuropathic pain phenotypes in patients with carpal tunnel syndrome: an open-label, randomized controlled study. *CNS Neurol Disord Drug Targets*. 2018;17(4):291–298. doi:10.2174/1871527317666180420143830
58. Giammusso B, Di Mauro R, Bernardini R. The efficacy of an association of palmitoylethanolamide and alpha-lipoic acid in patients with chronic prostatitis/chronic pelvic pain syndrome: a randomized clinical trial. *Arch Ital Urol Androl*. 2017;89(1):17–21. doi:10.4081/aiua.2017.1.17
59. Passavanti MB, Fiore M, Sansone P, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. *BMC Anesthesiol*. 2017;17(1):171. doi:10.1186/s12871-017-0461-9
60. Germini F, Coerezza A, Andreinetti L, et al. N-of-1 randomized trials of ultra-micronized palmitoylethanolamide in older patients with chronic pain. *Drugs Aging*. 2017;34(12):941–952. doi:10.1007/s40266-017-0506-2
61. Alejo-Martínez A, Bravo G, López-Muñoz FJ. N-Palmitoylethanolamide enhances antinociceptive effect of tramadol in neuropathic rats. *Biomed Pharmacother*. 2025;182:117760. doi:10.1016/j.biopha.2024.117760
62. Marcucci M, Germini F, Coerezza A, et al. Efficacy of ultra-micronized palmitoylethanolamide (um-PEA) in geriatric patients with chronic pain: study protocol for a series of N-of-1 randomized trials. *Trials*. 2016;17:369. doi:10.1186/s13063-016-1496-9

63. Iuvone T, Affaitati G, De Filippis D, et al. Ultramicronized palmitoylethanolamide reduces viscerovisceral hyperalgesia in a rat model of endometriosis plus ureteral calculosis: role of mast cells. *Pain*. 2016;157(1):80–91. doi:10.1097/j.pain.0000000000000220
64. Cristiano C, Avagliano C, Cuozzo M, Liguori FM, Calignano A, Russo R. The beneficial effects of ultramicronized palmitoylethanolamide in the management of neuropathic pain and associated mood disorders induced by paclitaxel in mice. *Biomolecules*. 2022;12(8):1155. doi:10.3390/biom12081155