Here is a comprehensive response to your query, with documents sorted by category and summarized in layman's terms:

1. PEA General Properties & Mechanisms

- "JBR.38.20240053.pdf"12
  - This review highlights Palmitoylethanolamide (PEA) as an endocannabinoid-like mediator with wide-ranging positive effects1. It's extensively studied for its anti-inflammatory, antimicrobial, immunostimulatory, neuroprotective, and pain-reducing properties, showing high tolerability and safety in both animals and humans1. PEA is suggested to have therapeutic benefits in many conditions, including neurological, psychiatric, ophthalmic, metabolic, cancer, kidney, liver, immune system, rheumatological, and digestive problems1. The review emphasizes PEA's multiple molecular targets and ways it acts, further supporting its use as an important dietary agent1. It also notes that PEA is a "non-typical" endogenous cannabinoid produced by the body when needed in response to various stimuli2.
- "MET2885-Hemp-PEA-Science-Review-IPAD.pdf"3...
  - This science review explains that the endocannabinoid system (ECS) is vital for regulating many bodily functions, including responses to stress, immune reactions, appetite, and brain health36. Research on the ECS has led to the discovery of not only endocannabinoids but also endocannabinoid-like lipid mediators such as PEA3. While these compounds share similar metabolic pathways, PEA does not directly bind to the classical cannabinoid receptors (CB1 and CB2)3. The review summarizes PEA's health benefits from human clinical studies, noting its neuroprotective effects in conditions like Amyotrophic Lateral Sclerosis (ALS) and mild cognitive impairment (MCI)5. For instance, a case report of sporadic ALS showed improved clinical outcomes with PEA and luteolin supplementation5.
- "PEA-Palmitoylethanolamide-useful-adjunct-Chemotherapy.pdf"7
  - This source indicates that PEA is involved in homeostatic (balancing) and traumatic injuries of the central nervous system (CNS)7. It also discusses the evolving understanding of PEA, from a non-specific resistance factor to an agonist of PPAR-alpha, and its current recognition as an effective nutraceutical7.
- "biomedicines-13-01271-1.pdf"8...
  - This overview describes PEA as a naturally occurring lipid mediator known for its diverse effects on brain protection (neuroprotection), managing long-lasting pain (chronic pain), and immune system regulation8. Its main actions come from activating a specific nuclear receptor called PPAR-alpha, and also indirectly affecting cannabinoid receptors (CB1 and CB2) and other targets like GPR55 and TRPV18. A key development is ultramicronized PEA (umPEA), which is much better absorbed by the body, improving its therapeutic effects8.
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UmPEA is particularly effective because it offers targeted, multi-pronged relief for different types of pain:

- For nociceptive pain (from tissue injury), umPEA acts by reducing inflammation, stabilizing mast cells, and stopping the release of inflammatory chemicals9.
- For neuropathic pain (from nerve damage), umPEA works by calming activated microglia (brain immune cells), reducing inflammatory chemicals, and making nerve cells less overly excitable9.
- For nociplastic pain (pain without clear tissue/nerve injury), umPEA's ability to cross the brain's protective barrier and influence brain immune cells (glia) is beneficial9.
  - UmPEA has a well-established safety record, making it a promising option alone or alongside standard anti-inflammatory and pain treatments8.
- "c66e3d6e8c4e6b6e842e6ee3a9e3ba240381.pdf"1112
  - This review positions Palmitoylethanolamide (PEA) as an endocannabinoid-like lipid mediator that is naturally found in the body and in certain foods11. It has been extensively documented for its anti-inflammatory, pain-relieving (analgesic), antimicrobial, immune-regulating (immunomodulatory), and brain-protective (neuroprotective) effects11. PEA is highlighted for its high tolerability and lack of side effects in both animals and humans11. Its ability to act on multiple molecular targets and influence various inflammatory chemicals provides therapeutic benefits across many areas, including immunity, brain health, allergies, pain control, joint health, sleep, and recovery11. The review also points out that PEA's previously poor absorption when taken by mouth has been improved by advanced delivery systems now available as food supplements11.
- "s40122-024-00685-4.pdf"13...
  - This review examines PEA's use in neuropathic pain management, which has been ongoing for over 20 years13. It covers PEA's effects in the body and how it is processed (pharmacodynamics and pharmacokinetics)13. The review delves into why PEA is effective for neuropathic and mixed pain, explaining its actions through the endocannabinoid system, specifically by interacting with cannabinoid receptors1314. It also highlights PEA's neuroprotective effects on mast cells and glial cells, which are important for both pain relief and neurodegenerative conditions14. The article mentions newer PEA formulations, like micronized and Equisetum-PEA, that aim to improve how well the body absorbs and uses PEA, thereby boosting its anti-inflammatory, antioxidant, and pain-relieving properties1314. The authors outline their comprehensive method for gathering information, including searching multiple databases and reviewing references to ensure complete coverage of PEA's role in chronic neuropathic and mixed pain15....
- "nihms37259.pdf"21

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This source states that anandamide (AEA) and its related compound, Palmitoylethanolamide (PEA), play a role in regulating many similar biological processes related to disease, such as pain, seizures, nerve damage (neurotoxicity), and inflammation21. Both AEA and PEA fit the definition of "lipid transmitters" because they are produced when stimulated, interact with specific targets, and are broken down by enzymes21. However, the source also suggests that AEA and PEA might work through separate signaling pathways, meaning they have different ways of being made, interacting with targets, and being inactivated21.
2. Pain Management (General & Neuropathic)
•
"094_karimi.pdf"22...
◦
This study explored the pain-relieving (antinociceptive) and anti-inflammatory effects of a modified version of PEA, called a morpholino analogue, using different pain tests in rodents22. In one test, doses of 50 and 100 mg/kg of this PEA analogue significantly reduced abdominal contractions, similar to the effects of diclofenac22. In other pain tests, the PEA analogue at these doses showed similar effects to morphine22. The results suggest that this PEA analogue has dose-dependent pain-relieving activity affecting both the central and peripheral nervous systems, indicating it could be a new pain medication that targets the body's own cannabinoid system22. The introduction mentions that while natural and synthetic cannabinoids have pain-relieving effects, there's a need to improve them to avoid side effects, especially those affecting the brain23.
•
"20240326-12658-ri7hnd.pdf"25...
◦
This clinical study evaluated the effectiveness of PEA for reducing pain intensity (measured by a numeric rating scale, NRS) and improving nerve health (measured by magnetic resonance neurography) in patients25. Most patients had moderate pain and moderate nerve involvement30. The study found a significant reduction in pain intensity in all treatment groups after three months29. PEA is described as a natural lipid that has neuroprotective, anti-inflammatory, and pain-relieving (analgesic) functions30. It's found in foods like soy lecithin, egg yolk, and peanut flour30.
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PEA works by:
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Modulating the endocannabinoid system, primarily by acting as an agonist for PPAR-alpha, a protein that regulates inflammation and pain30. This activation changes how genes are expressed, leading to anti-inflammatory and pain-relieving effects30.
▪
Having an anti-inflammatory effect by stopping the release of pro-inflammatory chemicals like TNF-alpha, interleukin 1 beta (IL-1β), and prostaglandins30. It also helps reduce brain and nerve inflammation by inhibiting mast cells and microglia, which in turn lessens pain and nerve-related symptoms30.
▪

Providing neuroprotection by helping nerve cells survive and slowing down nerve degeneration30. It also affects brain-derived neurotrophic factor (BDNF), which is important for nerve repair and adaptability30.

- Modulating ion channels, specifically interacting with TRPV1 channels, which helps control pain signals30.

- "2746e737017f8fa6ecc6b0398a4c27a54752.pdf"31...
  - This systematic review and meta-analysis aimed to evaluate the clinical evidence for PEA's effectiveness in managing various types of pain, including nociceptive (from tissue damage), musculoskeletal, and neuropathic (nerve-related) pain31. The review included studies on patients of any age, gender, and ethnicity suffering from pain, excluding animal studies, in vitro studies, case reports, and other review types32. It focused on studies that investigated PEA's effect on pain, excluding those on conditions like endometriosis, mouth pain, or irritable bowel syndrome if pain was not the primary outcome3637.
  - PEA is described as an endogenous fatty acid amide with antioxidant activity, believed to be produced in the body in response to injury31. It has diverse actions, including:
    - Indirectly modulating the endocannabinoid system by inhibiting an enzyme called fatty acid amide hydrolase (FAAH), which increases the levels of pain-relieving endocannabinoids31.
    - Activating the nuclear receptor PPAR-alpha31.
    - Activating the transient receptor potential channel of the vanilloid type 1 (TRPV1)31.
  - Preclinical research supports PEA's pain-relieving properties, particularly in different forms (micronized and ultramicronized) and in combination with other compounds, showing its role in modulating pain-related behaviors31. The meta-analysis found that PEA interventions showed efficacy in reducing pain intensity, though with high variability among studies38.

- "JPPXXPEAmorGbp23.pdf"4344
  - This study investigated the pain-relieving (antinociceptive) effects of PEA when injected locally in mice, comparing it to morphine (MOR) and gabapentin (GBP) in a formalin pain test43. The results showed that individual local injections of PEA, MOR, or GBP all reduced pain-related behaviors in a dose-dependent manner43.

- "LIT0043MIUS_PEA_Patient_Handout_INT.pdf"6
  - This handout explains that the Endocannabinoid System (ECS) is a complex system in the body that helps regulate many physiological functions, including how we respond to stress, our immune system, appetite, and brain health6. It mentions that minor pain can significantly impact

overall well-being and quality of life, and that people are exploring alternative approaches for pain relief6.

- "Lav-Balaton-AD-P-8.pdf"45...
  - This clinical study examined patients suffering from chronic pain due to various conditions like radiculopathy (nerve root pain), osteoarthrosis, herpes zoster infection (shingles), diabetic neuropathy, failed back surgery syndrome, and cancer46. Many of these patients were already receiving standard pain therapies (opioids, antidepressants, anticonvulsants, NSAIDs) but with unsatisfactory results45. PEA was given alongside these existing therapies46. The study noted that PEA can modulate mast cells and microglia, which are immune cells involved in pain processes48.
- "Lav-NevritinaL-RP-7 (2).pdf"49...
  - This source presents a meta-analysis on the efficacy of PEA for managing chronic pain across various conditions50. It also discusses the use of cannabinoids for chronic pain, noting that while drug trials support their use, they can have short-term adverse effects like fatigue, confusion, and somnolence4952. The meta-analysis used the visual analog scale (VAS) to measure subjective pain50. It aimed to answer key questions, including whether PEA is effective for pain, and if its dosing or duration of treatment are associated with increased effectiveness51.
- "Non-Neuronal Cell Modulation Relieves Neuropathic Pain..pdf"54...
  - This work investigated how the natural lipid PEA helps relieve neuropathic pain54. It focuses on whether PEA's pain-relieving effects involve changes in how non-nerve cells, specifically mast cells and microglia, behave54. These immune cells are known to release pain-causing substances that interact with neurons, contributing to chronic pain54. The study describes methods used to observe mast cell changes and measure NGF (Nerve Growth Factor) content in tissues5556.
- "Palmitoylethanolamide-and-hemp-oil-extract-exert-synergistic-anti-nociceptive-effect.pdf"57...
  - This study investigated the effectiveness of a full-spectrum hemp oil extract (HOE), alone or in combination with PEA, in mouse models of acute and chronic pain57. They found that HOE had only modest pain-relieving effects on its own5763. However, when low doses of HOE and PEA were combined, they produced a significantly greater-than-additive (synergistic) reduction in pain-related behaviors5763. The study also showed that combining HOE with PEA increased and prolonged the presence of PEA in the body57.
- "TOPAINJ-5-12.pdf"66
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This source notes that PEA has been studied since 1968, and its relationship with anandamide, another endocannabinoid, was described in the 1990s66. Research has shown that PEA can reduce pain behaviors in mouse models in a dose-dependent manner66. It also highlights PEA's ability to reduce the overactivity of mast cells, which are immune cells involved in inflammation and pain66.

- "pea-dolore.pdf"67...
  - This study investigated the effectiveness of PEA against neuropathic pain in mice with sciatic nerve injury, finding that daily PEA treatment reduced both thermal hypersensitivity and mechanical sensitivity to pain67. The results suggest that PEA's pain-relieving effects are mediated by CB1, PPAR-alpha, and TRPV1 receptors, possibly through an "entourage effect" where PEA boosts the levels of the endocannabinoid anandamide by slowing its breakdown67. Additionally, the study supports the idea that PEA acts by modulating local mast cell degranulation, which reduces the production of inflammatory mediators like TNF-alpha and nerve growth factors (NGF)67.
- "s13063-016-1496-9.pdf"70...
  - This document outlines a study protocol for N-of-1 trials (single-patient trials) to assess the effectiveness of ultramicronized PEA (um-PEA) for chronic pain, particularly in elderly patients7071. The main goal is to help decide on long-term treatment for individual patients70. The study plans to measure daily pain intensity using a visual numeric scale, track the daily need for pain medications, and evaluate the impact of pain on daily activities using a modified questionnaire7273.
- "s13643-018-0934-z.pdf"81...
  - This document describes the protocol for a scoping review (a broad overview of existing research) focusing on the clinical uses of PEA in managing chronic pain8186. It defines PEA as a naturally occurring fatty acid amide, similar to the endocannabinoid anandamide, which acts locally and has its levels regulated by enzymes like FAAH and NAAA82. The review aims to gather information on how PEA is used alone or with other drugs for pain, comparing it to standard treatments, and assessing pain reduction using various scales81....
- "e054282.full.pdf"93...
  - This systematic review and meta-analysis assessed the long-term and serious harms of medical cannabis for chronic pain93. While acknowledging that adverse events are common among medical cannabis users, it found very low certainty evidence that serious adverse events are less common93108. Crucially, the review highlighted that PEA was usually associated with few to no adverse events compared to other types of medical cannabis93108. The authors note that most studies were not designed to compare medical cannabis to other pain treatments, making direct comparisons difficult104.

3. Neurodegenerative Diseases & Neuroprotection

- "027681.pdf"112113
  - This source describes laboratory procedures used in studying brain tissue, including fixing (preserving) tissues with formaldehyde and preparing thin sections for analysis112. These sections are then used to look for markers related to brain inflammation (neuroinflammation) and activation of support cells called astrocytes (astrogliosis)112. One of the study's findings, illustrated in a figure, suggests that certain treatments, including PEA, might prevent or reduce problems with spatial memory after brain injury (anoxia-ischemia) in rats113.
- "1429799897_SkaperetalCNSND-DT_NeuroinflammationNeurocognitiveDisorders(2014).pdf"114...
  - This review focuses on the critical role of inflammation in brain and nervous system disorders (neuroinflammation) and its connection to conditions affecting thinking and memory (neurocognitive disorders)114115. It explains that cells of the immune system and the central nervous system (CNS) interact, with immune cells releasing substances that cause inflammation in response to injury114. This inflammation is a key feature in many neurological problems, including chronic pain, neurodegenerative diseases (like Alzheimer's), stroke, spinal cord injury, and neuropsychiatric disorders (like anxiety and depression)114115.
  - The review specifically highlights the roles of microglia and mast cells, two main immune cell types, in neuroinflammation114115. When these cells are unregulated, they can affect thinking ability115116. The document proposes that controlling these microglia and mast cells using natural lipid signaling molecules, such as PEA, could be a new way to treat cognitive decline linked to depression and Alzheimer's disease115.
  - It mentions that PEA has well-known neuroprotective and anti-inflammatory effects118. Furthermore, combining PEA with luteolin (a flavonoid known for improving memory and reducing anxiety) has shown even greater benefits than either molecule alone in various animal models118. For example, a co-ultramicronized PEA/luteolin combination:
    - Showed a significant antidepressant effect in a mouse model of anxiety/depression where PEA alone wasn't effective118.
    - Promoted the growth of new brain cells (neurogenesis) and nerve cell connections in the hippocampus, which can improve cognition118.
    - Normalized inflammatory markers and reduced neuronal death in a lab model of Alzheimer's disease118.
    - Significantly improved motor function and tissue changes after spinal cord injury in mice, where neither PEA nor luteolin alone was effective118.

- "1742-2094-9-49.pdf"124125
  - This study demonstrated that PEA can prevent astrocyte proliferation (the uncontrolled growth of brain support cells) and reduce nerve cell death in lab models that mimic Alzheimer's disease (exposed to amyloid-beta, Aβ)124. It also showed that PEA can decrease the activation of astrocytes and protect nerve cells in a part of the brain called the CA3 region of the hippocampus, which is important for memory, when exposed to Aβ125. These effects were observed to involve specific cell receptors known as PPAR-alpha and PPAR-gamma124125.
- "ACTA-91-07.pdf"126
  - This review discusses the shared features of various neurological disorders, such as Parkinson's disease, Alzheimer's disease, spinal cord injury, and stroke, which include abnormal protein clumping, oxidative stress (cell damage from unstable molecules), cell death (apoptosis), over-stimulation of nerve cells (excitotoxicity), problems with calcium balance inside cells, and inflammation126. It highlights the potential of natural plant compounds (phytochemicals) like Palmitoylethanolamide (PEA), hydroxytyrosol, and Bacopa monnieri extracts for their ability to protect brain cells and reduce inflammation in these conditions, suggesting them as new treatment options126.
- "Dialnet-SystematicReviewOfNeuroprotectiveActionsOfTheECPIn-10142941.pdf"127...
  - This systematic review analyzed the brain-protective (neuroprotective) and anti-inflammatory actions of Palmitoylethanolamide (PEA), particularly in a mouse hippocampal nerve cell line (HT-22) subjected to oxygen deprivation and reoxygenation127130. The goal was to see how these findings could be applied to patients with neurodegenerative diseases like Alzheimer's and Parkinson's127....
  - The review included 12 studies, divided into those on human patients and those on mouse models137138. Results from mouse models and patients focused on Alzheimer's and Parkinson's diseases127139.
  - Key findings suggest that PEA treatment, especially with antioxidant supplements, offers protective actions at the hippocampal level (a brain area crucial for memory) and helps regulate inflammatory proteins and cytokines127140. It also indicated a decrease in acetylcholine (ACh)127. The review concluded that PEA, alone or with other supplements like antioxidants, prevents cognitive neurological damage, sometimes linked to memory preservation140. It also reaffirmed the value of using the HT-22 neuronal line in mouse models for studying neurodegenerative diseases like Alzheimer's and Parkinson's, suggesting multiple effective alternative treatments using PEA140.
- "Dr_Maldonado.pdf"141142
  -

This research project investigated the brain-protective (neuroprotective) effects of oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) in animal models of Parkinson's disease141. These models use chemicals (6-OHDA and MPTP) to cause degeneration of dopamine neurons in a brain region involved in movement141. The project aimed to provide information for developing new therapeutic approaches for neuroprotection142.

- "JAD143039.pdf"143
  - This abstract highlights the diverse changes that occur in Alzheimer's disease (AD), suggesting that a treatment approach that is both brain-protective (neuroprotective) and reduces inflammation might be effective143. PEA has gained attention for its anti-inflammatory and neuroprotective qualities observed in AD animal models143.
- "Palmitoylethanolamide in Homeostatic and Traumatic Central Nervous.pdf"144145
  - This review examines the effect of PEA on the functions of glial cells (support cells in the brain) and how targeting these cells might lead to new treatments for neurodegenerative disorders144. PEA is thought to be neuroprotective because it helps prevent brain swelling, reduces inflammation, and limits cell death (necrosis and apoptosis)144. The attractive aspect of PEA's neuroprotective effect is its consistent impact on various defense mechanisms that are activated in cases of CNS damage145. Research suggests that PEA could be useful in treating conditions linked to CNS injury145.
- "e443e898638702bc6de8f0e328b231fd03f5.pdf"146
  - This source refers to pioneering work by Rita Levi-Montalcini in 1994, where she reported on the protective effects of PEA in central nervous system (CNS) damage146. She emphasized that PEA, and similar compounds, accumulate in damaged tissues during conditions like CNS and heart ischemia (lack of blood flow)146. These protective compounds are even synthesized by nerve cells when certain receptors are activated, indicating the body's own defense mechanism against nerve cell injury146.
- "fpsyt-13-1038122.pdf"147...
  - This systematic review and meta-analysis explores the therapeutic effect of PEA in cognitive decline and neurocognitive disorders (NCDs)147148. NCDs are characterized by reduced survival of nerve cells, and the review aims to clarify PEA's role by looking at both human and animal studies148149.
  - The review found that most human studies on PEA focused on its effects on cognitive function in various disorders like stroke, Parkinson's disease, Frontotemporal Dementia (FTD), and traumatic brain injury (TBI)162. For instance, PEA has been shown to improve memory and cognitive function in TBI patients when added to standard therapy150.
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In animal models, PEA was investigated for its anti-inflammatory and neuroprotective effects in models of Alzheimer's disease (AD) and vascular dementia (VaD), as well as its impact on cognitive functions like memory152.... For example, PEA administration in rats countered amyloid-beta (Aβ)-induced reactive gliosis (abnormal activation of glial cells) and improved neuronal integrity152. In VaD mice, PEA rescued injured hippocampal neurons and improved memory154155. In AD mice, PEA administration improved memory and had positive effects on neuroinflammation and neuroprotective factors156.

- Overall, the review highlights that NCDs are the conditions where PEA's use seems most supported by research, with strong evidence for its therapeutic effect on core cognitive symptoms and underlying neurobiological mechanisms168.

• "jcm-09-00428-v2.pdf"172173

- This study investigated the brain-protective (neuroprotective) and antioxidant effects of long-term (three months) ultramicronized PEA (um-PEA) treatment in an animal model of Alzheimer's disease (3xTg-AD mice)172. The results showed that when given by mouth, um-PEA was absorbed and reached the brains of the mice172. The treatment improved cognitive deficits, reduced brain inflammation (neuroinflammation) and oxidative stress, and lowered increased glutamate levels in the hippocampus (a brain area vital for memory) observed in the AD mice172. These findings support um-PEA's beneficial effects in Alzheimer's disease, and because PEA is already approved for human use, it suggests a potential for quick translation to clinical practice172.

• "npp201225.pdf"174175

- This source mentions that PPAR-alpha agonists (substances that activate the PPAR-alpha receptor) can protect cortical neurons from inflammatory mediators175. It also refers to methods for measuring lipid peroxidation (a type of cell damage) in mouse brains174. The context relates to mild cognitive impairment, suggesting that these protective mechanisms might be relevant for cognitive function175.

• "role-of-nacylethanolamines-in-the-neuroinflammation-ultramicronized-palmitoylethanolamide-in-the-relief-of.pdf"176177

- This review focuses on the effects of micronized and ultramicronized PEA (m- and um-PEA) in chronic pain and neuroinflammation, particularly in conditions like neurodegenerative diseases, stroke, spinal cord injury, diabetes, and neuropsychiatric disorders176. It highlights that chronic pain and neuroinflammation, when prolonged, can become destructive176. PEA is described as a natural lipid mediator that has neuroprotective and anti-inflammatory properties, activated by the body's own defense mechanisms in response to injury or inflammation176. Although PEA does not directly bind to classical cannabinoid receptors, it can indirectly enhance the effects of cannabinoids176. Its anti-inflammatory, pain-relieving, and neuroprotective actions are linked to the activation of PPAR-alpha176. The review notes that micronized and ultramicronized forms of

PEA allow it to be taken orally, making administration easier and more flexible for clinical studies176.

- "s41598-017-12529-7.pdf"178
  - This source provides references related to research on Alzheimer's disease, specifically mentioning studies on amyloidosis (abnormal protein deposits) and serum amyloid A protein, as well as the role of TNF (tumor necrosis factor) signaling in the central nervous system (CNS)178. It also references research on multiple sclerosis, implying connections between these conditions and neuroinflammation.

4. Specific Conditions

Olfactory Dysfunction

- "000539651.pdf"179180
  - This clinical study's diagram shows the flow of patients participating in a study involving PEA-LUT (Palmitoylethanolamide and Luteolin) for post-viral patients179. The study uses "Sniffin' Sticks" for olfactory (smell) testing, which includes three distinct 16-item subtests: odor threshold (T), odor discrimination (D), and odor identification (I)179. Scores from these subtests are combined to get a total TDI score, with a maximum of 48179. The source defines anosmia (complete loss of smell) as a score of 16 or lower, and hyposmia (reduced sense of smell) as a score below 30.75179.
- "s-0044-1786046.pdf"181...
  - This systematic review explored interventions for smell disorders such as hyposmia (reduced smell), anosmia (loss of smell), and parosmia (distorted smell)183. Most studies in the review originated from Egypt, Italy, and the United States, involving over 3,500 patients183. Common assessment tools used before and after interventions included the Visual Analogue Scale (VAS), the Sniffin’ Sticks Test (SST), and others183184. One study mentioned that PEA-LUT's anti-neuroinflammatory properties could support neuroplastic changes in olfactory treatment by creating a more favorable environment for regeneration185.
- "s00405-023-08085-8.pdf"186...
  - This study describes how olfactory function was assessed in patients with smell alterations after COVID-19186. Clinicians used the Sniffin’ Sticks identification test to evaluate smell, presenting patients with 16 common odors in a multiple-choice format187. Scores were used to categorize olfactory function: anosmia (score less than 7), hyposmia (score 7 to 13), or normosmia (score 14 or higher)187.
- "s00405-024-08548-6.pdf"189190
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This study focused on qualitative olfactory disorders (parosmia and phantosmia) in patients who experienced persistent smell issues after COVID-19189. Patients were asked about the presence of these disorders, and demographic data like age, sex, and other health conditions were collected189. The duration of the smell disorder was calculated from the time of a negative COVID-19 test189.

COVID-19 (Broader)

- "PEA+paper+Luca.pdf"191
  - This source provides a clear definition of COVID-19's clinical stages based on the British National Institute for Health and Care Excellence (NICE) guidelines191:
    - Acute COVID-19: Symptoms and signs within the first 4 weeks after infection191.
    - Ongoing symptomatic COVID-19 (sub-acute COVID-19): Effects lasting from 4 to 12 weeks after symptoms started191.
    - Post-COVID-19 syndrome (chronic COVID-19): Symptoms that continue for 12 or more weeks and can't be explained by another diagnosis191.
  - The term "long COVID" (or "long-haul COVID"), created by patients, includes both ongoing symptomatic and post-COVID-19 syndrome191.
- "US20220304954A1.pdf"192
  - This patent describes a method for treating COVID-19 infection by administering a mixture of ultramicronized PEA (PEA-um) and micronized PEA192. It specifically defines ultramicronized PEA as having a very fine particle size distribution, with most particles below 6 microns and above 0.5 microns192.
- "s10072-024-07566-w.pdf"193...
  - This systematic review investigated various interventions for "brain fog" symptoms in patients with long-COVID193. It notes that brain fog significantly reduces quality of life and makes it hard for individuals to return to their normal routines202. The review found that non-invasive brain stimulation and hyperbaric oxygen therapy show promising results, improving blood flow and brain activity202. Furthermore, both rehabilitation strategies and the administration of PEA-LUT (Palmitoylethanolamide and Luteolin) have been linked to improvements in brain fog symptoms202. The review suggests that future studies should explore combinations of these interventions and track their effects over longer periods202.
- "s12879-025-11131-x.pdf"203...
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This scoping review summarized available studies on therapeutic agents for Post-Acute Sequelae of COVID-19 (PASC), also known as long COVID203. It found that while there's heterogeneity in PASC symptoms, certain treatments showed promise204. Hyperbaric oxygen therapy (HBOT), for example, is thought to help by reducing inflammation, promoting tissue repair through growth factors, and improving mitochondrial function, which could alleviate PASC symptoms related to brain function and chronic fatigue209. The review highlights that HBOT can reduce acute phase inflammatory proteins and cytokines, and enhance growth factors209.

- "s41398-024-02771-9.pdf"210...
  - This study investigated the impact of stress and resilience in healthcare workers (HCW) during the COVID-19 pandemic by measuring changes in hair concentrations of stress hormones (cortisone) and endocannabinoids/endocannabinoid-like compounds like Palmitoylethanolamide (PEA)210211. The study found that levels of AEA, PEA, OEA, and SEA significantly decreased over the course of the pandemic210216. Notably, PEA levels were significantly higher in individuals with higher resilience but lower in those reporting higher anxiety210. The findings suggest that hair analysis of these compounds can serve as a non-invasive marker for stress, and that monitoring psychological health could be important for future hospital pandemic planning217.

Stroke

- "1476-511X-9-47.pdf"219...
  - This study aimed to determine the levels of endocannabinoids (AEA, 2-AG) and Palmitoylethanolamide (PEA) in the blood of human patients with acute ischemic stroke and to evaluate their relationship with clinical disability and stroke volume219220. It was the first to show elevated peripheral AEA levels in acute stroke patients221. The study found a significant link between AEA or PEA levels and neurological impairment: the greater the impairment, the higher these levels were221. However, no significant differences in AEA or PEA content were observed at later time points223. This research is important because while animal studies showed endocannabinoid involvement in stroke, human evidence was lacking221223.
- "s11481-025-10171-z.pdf"227...
  - This systematic review explores the effects of cannabinoids (CBs) on brain inflammation (neuroinflammation) following ischemic stroke in animal models227229. It highlights that inflammation is a significant part of stroke's progression, leading to damage to brain cells and the blood-brain barrier227. The review found that CBs show promising results in reducing neuroinflammation, limiting cell death, and improving neurological problems in these models227. It notes that many CBs work through CB2 receptors, which are closely involved in inflammatory processes234. While preclinical evidence is strong, translating these findings to human clinical settings is challenging due to the potential for CBs to cause anxiety, cognitive deficits, and psychosis227.
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"s12975-015-0440-8.pdf"240...
- This clinical study investigated the use of co-ultramicronized PEA/luteolin (co-ultraPEALut) in both animal models and human patients with stroke240244. Stroke is a leading cause of death and disability, and while restoring blood flow is key, it can also cause additional damage due to inflammation240. The study assessed various outcomes in patients, including stroke severity (Canadian Neurological Scale), cognitive abilities (Mini-Mental State Examination), spasticity, pain (Numeric Rating Scale), and independence in daily activities (Barthel Index)244. In animal models, co-ultraPEALut was found to reduce ischemic damage and neurological deficits242....

- "srep23481.pdf"247...
  - This study showed that systemic application of PEA in rats prevented or reduced the release of pro-inflammatory cytokines (inflammatory chemicals) in a model of cortical spreading depression (CSD)248. CSD is a phenomenon linked to conditions like stroke and migraine auras249. This suggests PEA's potential to counteract inflammation in these brain events248.

Spinal Cord Injury (SCI)

- "1742-2094-10-20.pdf"251...
  - This source details the methods used in a study involving spinal cord injury (SCI) in mice251. It describes how the injury was induced, how spinal cord tissues were processed for analysis, and how the extent of damage to the gray matter was scored using a six-point scale251252. It also explains the use of the Basso Mouse Scale (BMS) to evaluate motor recovery and disturbance in the animals' movement after injury253255. This kind of research helps understand conditions like SCI, where PEA (Palmitoylethanolamide) and PPAR (Peroxisome Proliferator-Activated Receptors) are relevant255.

- "1742-2094-10-91.pdf"256...
  - This source discusses the significant role of neuroinflammation in various neurodegenerative diseases, including spinal cord injury (SCI)256. SCI often leads to permanent neurological disabilities, and the inflammation it causes can further reduce functional recovery256. The study describes experimental methods, including administering co-ultramicronized PEA/luteolin to mice after SCI and assessing the resulting histopathological changes and motor function258. This research aims to identify new compounds to control inflammation after SCI256.

- "s12035-015-9328-6.pdf"261
  - This source explains that spinal cord injury (SCI) is an acute traumatic lesion to the nervous system elements in the spinal canal, leading to temporary or permanent changes in motor, sensory, or automatic functions261. It describes a "secondary injury" phase that follows the initial trauma, which can last weeks or months261. In this secondary phase, acute inflammation can become a chronic process, leading to a continuous influx of immune cells (neutrophils,

macrophages, lymphocytes, eosinophils) and causing further tissue destruction, scarring, and cell death through various mechanisms like necrosis, apoptosis, or autophagy261.

- "qt9vd1t3vz_noSplash_2b844fd66ea3ae478d755d476f4a3ff4.pdf"262...
  - This study investigated the effect of Palmitoylethanolamide (PEA) on secondary damage following experimental spinal cord injury (SCI) in mice262. SCI causes severe damage characterized by swelling (edema), immune cell infiltration (neutrophils), and production of inflammatory chemicals262. The study found that PEA treatment significantly reduced these harmful effects, showing less edema, fewer inflammatory cells, and reduced expression of inflammatory markers like FAS ligand265266. This protective effect is linked to PPAR-alpha activation262.

Diabetic Neuropathy / Renal Health

- "article-pdf-1730908653-1298.pdf"269
  - This review focuses on the potential of PEA therapy for diabetic nephropathy, which is a common kidney complication of diabetes269. It explains that high blood sugar in diabetes contributes to kidney damage and that the endocannabinoid system, widely present in kidney tissues, is linked to chronic kidney dysfunction269. The review highlights PEA's ability to produce powerful anti-inflammatory and antioxidant effects due to its many molecular targets269. While PEA is often studied for pain, this review emphasizes its beneficial effects on kidney tissues in diabetic conditions and calls for more clinical studies to confirm its kidney-protective effects in diabetic patients269.
- "s10787-022-01033-8.pdf"270...
  - This clinical study investigated the safety, tolerability, and effectiveness of PEA when given alongside prescribed diabetic and pain medications to relieve painful diabetic peripheral neuropathy (DPN)271. DPN is a common nerve disorder in diabetes, affecting up to 30% of patients and causing significant pain, disability, and falls270. Pain can range from electric shocks and stabbing to burning sensations and increased sensitivity270. The study used specific questionnaires like the Brief Pain Inventory Short Form for Diabetic Peripheral Neuropathy (BPI-DPN) and the Neuropathic Pain Symptom Inventory (NPSI) to assess pain severity and characteristics271. Secondary goals included seeing if PEA reduced inflammatory markers and improved mood and sleep quality271.

Ophthalmic Diseases (Glaucoma, Macular Degeneration)

- "US10350179.pdf"275...
  - This patent describes a combination of Palmitoylethanolamide (PEA) and lycopene (a powerful antioxidant) for the treatment of inflammatory diseases275. The invention can be formulated for oral, topical, ophthalmic (eye), rectal, vaginal, or parenteral (injection) use279. It specifically mentions its use in ophthalmic diseases such as Sjogren's syndrome, sympathetic ophthalmia,

uveitis, uveoretinitis, macular degeneration, or glaucoma277. The patent also states that naturally produced PEA helps ensure neuroprotection of nerve tissue and control neurodegeneration276.

- "US10987323.pdf"280...
  - This patent describes a combination of Palmitoylethanolamide (PEA) and lycopene for treating various inflammatory diseases, including acute and chronic forms283. These diseases can affect the skin (dermatological), eyes (ophthalmic), mucous membranes (mucosal, like Crohn's disease or mouth/genital inflammation), joints and connective tissues, as well as the peripheral and central nervous systems (PNS and CNS)281.... Specific CNS/PNS conditions mentioned include multiple sclerosis, neurodegenerative disorders, inflammatory processes associated with the CNS (such as Parkinson's disease, traumatic injuries, brain stroke), and neuropathies due to compression or trauma284285. The combination can be given daily, typically 2 to 4 times per day, at a dosage range of 0.1 to 50 mg per kg of patient body weight285.
- "i1552-5783-53-8-4416.pdf"286
  - This source discusses how cannabinoids (compounds found in cannabis) have been shown to lower eye pressure (intraocular pressure, IOP) and increase the outflow of fluid from the eye (aqueous humor)286. It notes that both CB1 and CB2 cannabinoid receptors are found in parts of the eye involved in fluid outflow, such as the ciliary body and trabecular meshwork286. Endocannabinoids like AEA and 2-AG are also shown to increase aqueous humor outflow286.
- "i1552-5783-54-2-968.pdf"287
  - This source references the finding of endocannabinoids in human eye tissues and, importantly, mentions a clinical trial that demonstrated the ocular hypotensive effect (eye pressure-lowering effect) of oral Palmitoylethanolamide (PEA)287.
- "s41598-020-67527-z.pdf"288289
  - This study examined the effect of PEA in patients, including measuring their intraocular pressure (IOP) using Goldmann tonometry and visual field using the Humphrey Visual Field test288. These tests are commonly used to diagnose and monitor glaucoma288. The study aimed to assess the ocular hypotensive (eye pressure-lowering) effect of PEA289.

Gastrointestinal Health

- "131287709.pdf"290291
  - This source references studies on how PEA improves colon inflammation by activating a protein called PPAR-alpha through certain pathways involving gut immune cells (enteric glia) and Toll-like receptor 4 (TLR4)290. It also mentions that cannabidiol and anandamide can reduce damage to the gut lining in human colon tissue samples290. The broader context points to the

role of naturally occurring fatty acid ethanolamides in the gastrointestinal tract, including their influence on food intake291.

- "Fip+D'Antongiovanni+et+al+2021.pdf"292...
  - This study investigated whether PEA could counteract the buildup of proteins linked to neurodegenerative disorders (like Aβ, t-tau, and α-syn) and restore normal cellular activity (citrate synthase activity) in the colon of SAMP8 mice292293. It also looked at how PEA affects intestinal inflammation (measured by levels of TLR-4 and IL-1β) and the activation of support cells in the gut (enteric gliosis, measured by S100-β) that are associated with cognitive decline294. The results showed that PEA effectively countered the accumulation of these proteins and reduced both intestinal inflammation and enteric gliosis293294.
- "nihms598043.pdf"295
  - This study investigated the effect of the cannabimimetic Palmitoylethanolamide (PEA) in a rat model of intestinal radiation mucositis (inflammation of the gut lining due to radiation)295. The research was driven by the understanding that endocannabinoids play a role in regulating intestinal inflammation295.
- "izz017.pdf"296...
  - This study demonstrated for the first time in humans that PEA and cannabidiol (CBD) help reduce intestinal permeability (leaky gut) in the colon, which has implications for conditions like inflammatory bowel disease (IBD)296300. The gut normally acts as a selective barrier, and inflammation can compromise this barrier, allowing harmful substances to enter the bloodstream296. The study used a "lactulose-mannitol test" to measure gut permeability in healthy participants treated with aspirin (to induce mild inflammation) and either placebo, CBD, or PEA300. The results showed that both PEA and CBD significantly prevented increases in gut permeability300. This effect may involve changes in water channels (AQP), tight junctions (TJ), and receptor expression in the gut lining300.

Headache/Migraine

- "3938640.pdf"302...
  - This study assessed the effectiveness of a treatment in reducing migraine attack frequency and intensity302. Patients classified their attack intensity as mild, moderate, or severe302. The primary goals were to achieve a reduction of more than 50% in attack frequency and at least a one-point reduction in pain intensity302. The study included patients with episodic migraine without aura, and none were receiving preventative migraine treatment, though NSAIDs were used for acute headaches303. The sources include references to mast cells, anandamide, and PEA, suggesting a connection to their mechanisms305.
- "PEA-IMCRJ-Palmitoylethanolamide-pea-for-nummular-headache.pdf"306

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This case report describes a patient with nummular headache, a specific type of localized head pain306. The case showed an excellent response to preventive therapy that included PEA, along with another drug used for nerve-related pain306. This response supports the theory that this type of headache is due to an activation of the trigeminal vascular system306.
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