



DOSSIER · SUBSTANCE

Palmitoylethanolamide (PEA)

This page organises the works on palmitoylethanolamide, an endogenous fatty acid amide that is supplied as a nutraceutical. The largest part of the research concerns pain and inflammation. It is striking how often combination preparations have been studied — as a result, the effect of the single substance can rarely be separated.

118

STUDIES IN
TOTAL

88

IN HUMANS

60

OF WHICH
CONTROLLED

10

IN ANIMALS

1

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a
comparison group

PLAUSIBLE

supported by mechanism, animal
studies or observation

HYPOTHESIS

a likely connection that still needs to
be tested

Palmitoylethanolamide (PEA) at a Glance

ORIGIN:
Palmitoylethanolamide, abbreviated as PEA, is an endogenous fatty acid amide relative that the studies describe as an anti-inflammatory messenger substance of the body; it is administered as a nutraceutical. Since 1957, PEA has been known as a dietary component that is formed and broken down in animal cells via several enzymes. Since the work of Nobel laureate Levi-Montalcini in 1993, the research focus has been on neuropathic pain conditions.

EVIDENCE BASE:
118 evaluated studies · 60 controlled human studies · 28 observational studies · 9 review articles · 10 animal studies · 0 cell culture studies

STRONGEST EVIDENCE:

- **Proven:** The 2023 meta-analysis on chronic pain pooled 11 randomised studies with 774 patients; the pooled result showed a standardised mean difference of 1.68 (95 % CI 1.05 to 2.31).
- **Plausible:** In a placebo-controlled study of 111 adults with knee osteoarthritis, the WOMAC total score decreased under 300 mg (p = 0.0372) and 600 mg PEA (p = 0.0012) versus placebo over eight weeks.
- **Plausible:** The 2015 review on nerve compression syndromes cites a number needed to treat of 1.5 for sciatic pain after three weeks of treatment, based on 636 patients.
- **Plausible:** A 2016 review examined 16 clinical studies and one meta-analysis; for treatment durations up to 49 days the data argue against serious adverse effects from an incidence of 1/200.
- **Plausible:** In a preliminary randomised double-blind study, 600 mg ultramicrosised PEA twice daily over 60 days significantly reduced burning sensation in burning-mouth syndrome (p < 0.0132).

LIMITATIONS:

- Combination studies with luteolin, trans-polydatin, cannabidiol or an antipsychotic do not permit conclusions about PEA alone; the contribution of the individual substance remains open.
- Direct comparisons of microsised and ultramicrosised PEA are still outstanding; which preparation is superior remains a testable question.
- Two studies determined endogenous PEA as a marker, not supplemented PEA; whether supplementation reproduces the observed shifts there has not yet been examined.

CLASSIFICATION:
PEA is an endogenous fatty acid amide messenger substance that is administered as a nutraceutical; the most robust level of research is reached for chronic pain.

1. What Palmitoylethanolamide Is

Palmitoylethanolamide, abbreviated as PEA, is an **endogenous fatty acid amide relative**. The studies describe it as an **anti-inflammatory messenger substance of the body**; it is administered as a **nutraceutical**, that is, as a dietary supplement and not as a classic medicinal product. The review literature names binding to the **PPAR-α receptor** as the mechanism of action; earlier classifications referred to non-specific resistance enhancement. Related studies address **inhibition of fatty acid amide hydrolase (FAAH)** and **cannabidiol**, that is, enzymes and substances of the same fatty acid amide metabolism. The captured studies cover pain, inflammation, metabolism, cognition, immune system, oncology and viral infections. Two things must be distinguished for classification: the endogenous messenger substance and the administered preparation.

Decisive for evaluation is the **preparation form**. The studies distinguish between **microsised** and **ultramicrosised** PEA; finer milling is said to improve absorption, yet direct comparisons of the preparations belong to the open questions. Some studies test PEA not alone but in **combination** with luteolin, with trans-polydatin or with cannabidiol; another tests PEA as an adjunct to an antipsychotic. No conclusion about the single substance can be drawn from such approaches. Added to this is the **diversity of endpoints**: pain intensity and questionnaires, cytokine levels, sleep-wake rhythm, sense of smell or permeability of intestinal cells in the laboratory are recorded. Laboratory values and questionnaires are markers, not disease course. Anyone who places the studies side by side is therefore comparing different preparations, combinations and endpoints.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by field of application, with population, duration, preparation, measure and result as reported in the original studies. Numbers appear only where the study states them.

Distribution of **controlled human studies** by field of application — the numbers are not additive, as one study may be assigned to several fields:

FIELD OF APPLICATION	CONTROLLED STUDIES
Inflammatory processes	30
Safety and tolerability	26
Metabolism	18
Cognition and psyche	18

FIELD OF APPLICATION	CONTROLLED STUDIES
Musculoskeletal system	16
Fatigue and stress	16
Immune system	9
Oncology	6

Metabolism

A controlled study examined whether the analgesic effect of isometric muscle work operates via opioid and endocannabinoid mechanisms in 58 men and women (mean age 21 years). After double-blind administration of 50 mg naltrexone or placebo, participants performed three minutes of submaximal isometric exercise in three sessions; blood was taken before and after exercise and the intensity of heat pulses, pressure pain threshold, pressure pain rating and temporal summation of heat pain were recorded. Circulating concentrations of N-arachidonylethanolamine and 2-arachidonoylglycerol as well as the related lipids oleoylethanolamide, palmitoylethanolamide, N-docosahexaenylethanolamine and 2-oleoylglycerol rose significantly after exercise ($P < .05$). Pressure pain thresholds rose, pressure pain ratings and temporal summation also fell significantly ($P < .05$), with no difference between placebo and naltrexone conditions ($P > .05$). Endogenous PEA was measured as a marker, not supplemented PEA.

A randomised, double-blind study in 42 patients with total knee arthroplasty tested whether intrathecal morphine reduces postoperative pain and how the levels of the weakly analgesic endocannabinoids anandamide and 2-arachidonoylglycerol as well as the related lipids palmitoylethanolamide and oleoylethanolamide behave in this context¹⁸. The intervention consisted of 200 µg intrathecal morphine or placebo at the time of spinal anaesthesia; pain was measured in the first four hours after surgery, serum levels of anandamide, 2-AG, PEA, OEA and cortisol at baseline and four hours postoperatively. Morphine reduced postoperative pain four hours after surgery versus placebo ($p = 0.005$) and reduced systemic opioid consumption ($p = 0.001$). At baseline, morphine led to a significant reduction in anandamide, 2-AG and OEA, but left PEA and cortisol levels unaffected; under placebo, 2-AG levels rose four hours after surgery, while patients receiving morphine showed reductions in anandamide, PEA and OEA versus placebo. Here too, PEA was determined as an endogenous marker, not given as a preparation.

HYPOTHESIS That endogenous PEA and related fatty acid amides fluctuate measurably during muscle work and under the influence of morphine suggests that they are involved in endogenous pain modulation. Whether supplementation with PEA influences this regulatory circuit in the same direction has not been shown; both studies examined concentrations in the blood, not substitution. The obvious next question is whether the shifts observed during exertion and under morphine can be reproduced with exogenous administration.

Safety and Tolerability

A 2016 review examined 16 clinical studies, six case reports or pilot studies and one meta-analysis on PEA as an analgesic and tested the repeatedly stated assumption that PEA is effective and free of adverse effects². For treatment durations up to 49 days the available clinical data argue against serious adverse drug reactions at an incidence of 1/200. For treatments exceeding 60 days the number of treated patients is insufficient to exclude an incidence of adverse drug reactions below 1/100. The six published randomised clinical studies are, in the authors' assessment, of varying quality; identified problems include presentation of data without information on dispersion and the absence of reports at time points other than the final measurement. Direct comparisons of non-micronised and micronised formulations are still outstanding; which formulation is superior remains a testable question. The authors note that the clinical data support an analgesic effect of PEA.

In burning-mouth syndrome a preliminary randomised double-blind controlled study tested ultramicrosized PEA¹¹. Patients with a burning intensity above 4 on the Numeric Rating Scale were enrolled and randomised to placebo or 600 mg ultramicrosized PEA twice daily for 60 days. Assessments were performed at baseline, after 30 and 60 days and four months after the end of treatment; change in burning sensation over time was analysed with a generalised linear mixed model. Of 35 patients judged eligible, six discontinued before the end of treatment. At the end of active treatment a statistically significant reduction in burning sensation ($p < 0.0132$) was observed in the PEA group compared with placebo. No adverse effects of active treatment were observed or reported by patients or physicians. The authors themselves describe the work as preliminary.

Viral Infections

In outpatients with confirmed COVID-19 and post-infectious olfactory dysfunction persisting for at least 90 days after a negative SARS-CoV-2 test, a randomised controlled pilot study examined whether a supplement of PEA and luteolin supports recovery of olfaction³. Patients with pre-existing olfactory disorders were excluded. Randomisation was to twice-daily olfactory rehabilitation alone or to weekly olfactory rehabilitation plus daily oral administration of the supplement. Olfactory performance was recorded with Sniffin' Sticks at baseline and 30 days after the start of treatment, supplemented by data on sex, age and time since infection; variances of Sniff scores between groups over time were compared with the Kruskal-Wallis test and associations with sex or duration with Spearman correlation coefficients. Because the combination of PEA and luteolin was investigated, the study permits no statement about PEA alone. It remains to be clarified what contribution PEA makes to any possible recovery.

A 2013 review traces that PEA has been a known dietary constituent since 1957, is formed and degraded in animal cells by several enzymes, and that more than 350 PubMed-referenced papers exist on its physiological properties³³. Since the work of Nobel laureate Levi-Montalcini in 1993 the focus of PEA research has been on neuropathic pain states and mast-cell disorders. The paper recalls that already in the previous century six clinical studies involving nearly 4000 people specifically examined PEA as therapy for influenza and the common cold, before the mechanism of action was elucidated by Levi-Montalcini. The authors regard these results as support for the efficacy and safety of PEA in influenza and respiratory infections. A re-examination of these findings with contemporary methods is still outstanding.

Inflammatory Processes

In a randomised, double-blind, placebo-controlled study ultramicronised PEA was tested in addition to interferon- β 1a therapy in clinically defined relapsing-remitting multiple sclerosis ⁴. Primary objectives were whether patients receiving um-PEA experienced improvement in pain and a reduction in erythema width at the IFN- β 1a injection site as well as an improvement in quality of life. Secondary outcomes after one year of treatment included serum levels of interferon- γ , tumour necrosis factor- α and interleukin-17, plasma N-acyl ethanolamine levels, course on the Expanded Disability Status Scale, and safety and tolerability. The authors report that patients with MS perceived an improvement under um-PEA. It remains open whether the perceived improvement is reflected in the secondary laboratory and course measures.

In 111 adults with mild to moderate knee osteoarthritis a single-centre, double-blind, placebo-controlled study compared 300 mg PEA, 600 mg PEA and placebo, each given daily in divided doses b.i.d. for eight weeks ⁵. The primary endpoint was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); secondary outcomes included Numerical Rating Scales for pain, the Depression Anxiety Stress Scale, the Perceived Stress Scale, the Pittsburgh Sleep Quality Index, the Short Form Health Survey, consumption of rescue analgesia and a clinical safety assessment. Compared with placebo the WOMAC total score decreased in the 300-mg group ($p = 0.0372$) and in the 600-mg group ($p = 0.0012$), the WOMAC pain score (300 mg: $p = 0.0074$; 600 mg: $p < 0.001$), the WOMAC stiffness score (300 mg: $p < 0.0490$; 600 mg: $p = 0.001$) and the WOMAC function score in the 600-mg group ($p = 0.033$). NRS ratings for "worst pain" and "least pain" were significantly reduced in the 300-mg group ($p < 0.001$, $p = 0.005$) and in the 600-mg group.

PROVEN A systematic review and meta-analysis of 2023 searched MEDLINE and Web of Science for double-blind randomised controlled trials comparing PEA with placebo or active comparators in chronic pain ⁶. Of 253 identified articles, 11 were included in the narrative synthesis and meta-analysis; together they describe 774 patients. In the pooled estimate PEA reduced pain scores versus the comparators with a standardised mean difference of 1.68 (95 % CI 1.05 to 2.31). Quality of life, functional status and adverse effects were presented narratively. Because placebo and active comparators are pooled together as the comparator, the pooled figure does not allow inference about the magnitude of the difference from placebo alone.

A 2015 review summarises all clinical studies that have tested PEA in nerve-compression syndromes, namely sciatic pain and pain in carpal-tunnel syndrome ⁸. In a pivotal double-blind, placebo-controlled study in 636 patients with sciatic pain the number needed to treat for a 50 % pain reduction from baseline was 1.5 after three weeks of treatment. Drug interactions or troublesome adverse effects have, according to the authors, not been described to date. An independent replication of the NNT is still outstanding.

In healthy volunteers a randomised, placebo-controlled, double-blind crossover study examined the mechanism of action of PEA ¹⁰. Fourteen healthy volunteers took 3×400 mg PEA per day or placebo for four weeks. The pain model was repeated phasic heat application, which is suitable for investigating analgesic and antihyperalgesic effects in healthy subjects; parameters of peripheral and central sensitisation and of pain modulation were recorded. After PEA treatment repetitive heat pain was significantly reduced and cold-pain tolerance was significantly prolonged; pressure-pain tolerance and conditioned pain modulation were increased, while the wind-up ratio and the mean extent of allodynia were significantly reduced. These experimental endpoints are not clinical pain measures; whether the same mechanisms are found in patients with chronic pain remains open.

In 70 patients with type-1 and type-2 diabetes and diabetic peripheral neuropathic pain a single-centre, quadruple-blind, placebo-controlled study examined 600 mg PEA or placebo daily for eight weeks, with a completion rate of 94 % ¹⁵. Primary endpoints were neuropathic pain and specific pain types, recorded with BPI-DPN and NPSI; secondary outcomes included sleep quality (MOS Sleep Scale), mood (DASS-21), glucose metabolism and inflammation. Compared with placebo the BPI-DPN total pain score and pain interference as well as the NPSI total score and its subscales except evoked pain ($P = 0.09$) decreased significantly ($P \leq 0.001$). The MOS Sleep Problems Index and its subscales improved significantly ($P \leq 0.001$), DASS-21 depression scores decreased ($P = 0.03$), while anxiety and stress scores did not. Interleukin-6 and elevated C-reactive protein were significantly reduced in the PEA group ($P = 0.05$); these laboratory values are not to be read as clinical effects.

A 2012 case series describes the use, possible efficacy and safety of PEA in various syndromes with chronic pain that respond poorly to standard therapies, including diabetic neuropathy, chemotherapy-induced peripheral neuropathy, carpal-tunnel syndrome, sciatic pain, osteoarthritis, back pain, failed-back-surgery syndrome, dental pain, neuropathic pain after stroke and multiple sclerosis, chronic pelvic pain, post-herpetic neuralgia and vaginal pain ³⁴. The described courses are experiences from use without a control group, and systematic recording of these syndromes is still outstanding.

In 80 patients with fibromyalgia syndrome the additional benefit of PEA to a combination of duloxetine and pregabalin was examined in two steps ³⁶. First, 45 patients received duloxetine and pregabalin for six months in a retrospective observation; subsequently 35 patients began the same dosage plus micronised and ultramicronised PEA for three months in a prospective observation. Positive tender points, evoked pain and pain intensity were recorded at baseline and after three and six months. The retrospective group showed a decrease in positive tender points after three months. Because PEA was administered here only in addition to two analgesics, the study permits no statement about PEA as a single agent.

A case-control study compared concentrations of arachidonylethanolamide and 2-arachidonoylglycerol as well as the related lipids oleoylethanolamide, palmitoylethanolamide and stearoylethanolamide in 104 women with fibromyalgia and 116 healthy controls ³⁸. All participants rated pain, anxiety, depression and current health status; associations between lipid concentrations and clinical assessments were analysed multivariately and bivariate. OEA, PEA, SEA and 2-AG were significantly higher in women with fibromyalgia than in healthy controls; for OEA and SEA significance remained after controlling for body-mass index and age. 2-AG correlated positively with duration of fibromyalgia and body-mass index and to some extent negatively with pain, anxiety, depression and health status. These cross-sectional data describe levels, not causes; whether the elevated PEA values represent an enhanced endogenous response is an open question.

A 2021 review classifies PEA as an endocannabinoid-like lipid mediator with extensively documented anti-inflammatory, analgesic, antimicrobial, immunomodulatory and neuroprotective properties that is well tolerated in animals and humans ³⁹. PEA acts on several molecular targets and modulates a variety of inflammatory mediators; the previously considered major obstacle of poor oral bioavailability has been overcome by advanced delivery systems. The statements are based on the cited literature, not on new original data. A systematic review of 2020 places regulation of neuroinflammation via non-neuronal cells at the centre ⁴⁰: mast cells in the central nervous system and periphery as well as microglia at spinal and supraspinal levels are in close functional relationship with neurons, and control of neuroinflammation depends, according to this view, on local "on-demand" synthesis of PEA and related endocannabinoids. If the balance between synthesis and degradation is shifted in favour of reduced synthesis or increased degradation, the non-neuronal cells may no longer behave appropriately. A measurement confirming this mechanism in humans is still outstanding.

A 2022 review traces the use of PEA in neurodegenerative diseases ⁴¹. PEA belongs to the class of N-acyl ethanolamines and was first isolated from soya lecithin, egg yolk and peanut meal; it is used in various neuropathic pain conditions such as fibromyalgia, osteoarthritis and carpal-tunnel syndrome. Micronised and ultramicrosised forms, intended to increase bioavailability and efficacy, have prompted a series of studies examining PEA as a therapeutic agent in neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's disease. The paper summarises in-vitro, in-vivo and human studies and presents no new original data.

A 2013 review places the six decades of PEA research within the sociological concepts of Ludwig Fleck and Thomas Kuhn ⁴². PEA was identified in the 1950s as a therapeutic principle with anti-inflammatory properties; since 1975 its analgesic properties have been investigated in various chronic pain states; since 2008 it has been available as a food supplement. According to the paper, the discovery of the cannabinoid receptors and the nuclear peroxisome-proliferator-activated receptors was the prerequisite for understanding the analgesic and anti-inflammatory activity of this endogenous fatty-acid amide. A 2022 review is devoted to the ALIAMides in small-animal medicine and honours Francesco della Valle, who first advocated this "according-to-nature" approach ⁴³. The name of the substance family derives from the mechanism of action, Autacoid Local Injury Antagonism; PEA as the parent molecule is formed locally on demand from a cell-membrane precursor to control immuno-inflammatory cell responses and to limit chronic non-resolving inflammation. Sister compounds such as adelmidrol and palmitoylglucosamine share the mechanism of action and can raise endogenous PEA levels; their bioavailability is addressed by reducing particle size, for example by micronisation. The authors note that further data are needed and see in the ALIAMides a new, promising approach for the health of dogs and cats.

Fatigue and Stress

In 42 patients awaiting surgery for carpal-tunnel syndrome and suffering from sleep disturbances and pain, an open controlled study tested ultramicrosised PEA ⁷. Patients were randomised into two groups; one received 600 mg ultramicrosised PEA twice daily in the pre- and postoperative phase, the other received no treatment apart from surgery. The primary endpoint was sleep quality, assessed with the Pittsburgh Sleep Quality Index; secondary outcome was pain intensity on the Numeric Rating Scale. At the end of the preoperative phase (T1) a highly significant improvement in sleep quality ($p < 0.0001$) with increase in continuous sleep time as well as decrease in sleep latency and sleep disturbances and a significant alleviation of pain symptoms ($p < 0.0001$) were observed in favour of the treated group. The study is open-label; no placebo group was included; the authors themselves describe the results as preliminary. Whether the effect on sleep is mediated by pain relief remains to be examined.

Further Investigations

A meta-analysis examined the clinical efficacy of the combination of micronised PEA and trans-polydatin in endometriosis-related chronic pelvic pain ⁹. PubMed, SCIELO, Scopus and AJOL were searched systematically; randomised and observational studies reporting a visual analogue scale or comparable measure in endometriosis patients were included. The mean improvement in VAS values at enrolment and after three months of follow-up was compared. Four studies were available, which the authors themselves describe as of poor quality. Administration of 400 mg micronised PEA and 40 mg trans-polydatin twice daily for three months produced a clinically relevant improvement in chronic pelvic pain and dysmenorrhoea as well as a limited improvement in deep dyspareunia in the heterogeneous sample; no clinically relevant improvement was found for dyschezia. The combination, not PEA alone, was tested.

A systematic review and meta-analysis of 2022 examined PEA in nociceptive, musculoskeletal and neuropathic pain ¹². Search, selection and analysis followed the PRISMA-2020 recommendations; the primary endpoint was pain reduction on a pain scale, secondary endpoints were improvement in quality of life and functional parameters. In a total of 933 patients efficacy of PEA versus control was shown ($p < 0.00001$), particularly in six studies in addition to the two included randomised double-blind studies. The authors downgrade the results because of high heterogeneity of the studies ($I^2 = 99\%$) and point out that the funnel plot suggests publication bias. Also reported are a reduction in the need for rescue medication as well as improvements in function, neuropathic symptoms and quality of life. Replication in a pre-stratified sample is still outstanding.

Patients were randomised 1:1 and received either ultramicrosised PEA tablets of 300 mg twice daily for six months or no treatment. Best-corrected visual acuity, intraocular pressure and visual field test were recorded at baseline and at the end of the six-month follow-up; at baseline there were no significant differences between the groups. After six months the treatment group showed a significant reduction in intraocular pressure (from 14.4 ± 3.2 mm Hg to 11.1 ± 4.3 mm Hg, $p < 0.01$); visual acuity did not change significantly in either group. Visual field parameters deteriorated compared with baseline values (MD: -7.65 ± 6.55 dB vs. -4.55 ± 5.31 dB, $p < 0.001$; PSD: 5.21 ± 4.08 dB vs. 3.81 ± 3.02 dB, $p < 0.02$), while no significant changes occurred in the untreated group. A generalised linear model attributed the final intraocular pressure, MD and PSD solely to systemic PEA treatment ($p < 0.01$ each). Whether the finding is confirmed in a blinded study with a larger number of cases remains to be seen.

Twenty women with vestibulodynia were randomised and received oral 400 mg PEA and 40 mg transpolydatin or placebo twice daily for 60 days; all patients also followed a TENS programme according to a self-applied home protocol ³⁷. Visual analogue scale, Marinoff score for dyspareunia and current perception threshold in the vulvar vestibulum were recorded at baseline and at the end of treatment; on average the patients completed 26.7 TENS sessions. All scores improved significantly in both groups, yet the extent of improvement was similar between the groups (VAS $p < .57$; dyspareunia $p < .38$). A regression analysis of symptoms in relation to disease duration suggested the therapy was more effective. Because both groups received TENS, the contribution of the TENS protocol cannot be separated from that of the combination.

Cognition and Psyche

In an eight-week, double-blind, placebo-controlled study, patients with stable schizophrenia were randomised 1:1 and received, in addition to a stable risperidone dose, either 600 mg PEA twice daily or a matching placebo ¹³. Measurement time points were baseline as well as week 4 and week 8; the Positive and Negative Syndrome Scale, the Extrapyramidal Symptom Rating Scale and the Hamilton Depression Rating Scale were recorded, with the primary endpoint being the change in the negative subscale. A total of 50 participants completed the study, 25 per group; baseline characteristics were comparable ($p > 0.05$). For negative symptoms a significant time-by-treatment interaction effect was found ($p = 0.012$) in the sense of greater symptom improvement in the PEA group, while positive symptoms and depressive symptoms behaved similarly between the groups ($p > 0.05$). The safety of the interventions was monitored during the study. Whether the effect on negative symptoms persists beyond eight weeks remains open.

A review of translational evidence in depression examined the question of whether PEA has antidepressant effects ¹⁴. According to the review, PEA binds not only to the peroxisome proliferator-activated receptor alpha but also to the G-protein-coupled receptor 55 and with weak affinity to the cannabinoid receptors CB1 and CB2. In preclinical studies PEA showed antidepressant activity in animal models of depression as well as of depression associated with

neuropathic pain and traumatic brain injury; under stress conditions PEA is elevated. A randomised double-blind study in depressed patients suggested a rapid antidepressant effect of PEA. The work is a bibliographic review. An independent confirmation of this clinical observation remains to be seen.

Oncology

For tumour-associated pain the 2017 N-of-1 studies provide a paper that examined chronic pain in older people but explicitly excluded cancer¹⁶. Randomised, blinded N-of-1 trials with two three-week comparisons of ultramicronised PEA versus placebo, separated by two-week washout phases, were tested. Participants were ambulatory patients aged 65 years and older with chronic, non-tumour-related and non-ischaemic pain in the back, joints or limbs; they received 600 mg um-PEA or placebo twice daily. Pain intensity on an 11-point scale and functional impairment with the Back Pain Functional Scale were measured; in addition, the effect of each N-of-1 trial on the clinician's treatment intention and safety was recorded. Ten of eleven eligible patients consented over seven months (all female, mean age 83.2 years, SD 4.6). Three patients discontinued: one because of diarrhoea under placebo, one because of low adherence and one because of an intercurrent pneumonia. In the mixed-method analysis two patients showed a small statistically significant effect in favour of um-PEA, with an effect size of 8 %. Whether PEA is effective in tumour-related pain was not examined in this work and remains an open question.

Musculoskeletal System

A 2016 study examined how PEA influences acetylcholine currents at muscle membranes from ALS patients and at human acetylcholine receptors³⁵. The starting point was the observation that PEA altered the clinical condition in an ALS patient and improved muscle strength and respiratory efficiency. By microtransplantation of muscle membranes from selected ALS patients into *Xenopus* oocytes it was shown that PEA reduced the desensitisation of acetylcholine-evoked currents after repeated neurotransmitter application, the so-called rundown; the same effect occurred with muscle samples from denervated, non-ALS control patients. Expression of human recombinant $\alpha 1\beta 1\gamma\delta$ - and $\alpha 1\beta 1\epsilon\delta$ -acetylcholine receptors in *Xenopus* oocytes showed that PEA selectively influenced the rundown of ACh currents at ϵ -AChRs. Quantitative PCR revealed a marked upregulation of the $\alpha 1$ subunit in muscle from ALS patients compared with non-ALS patients, without differential expression of other subunits. Clinically, forced vital capacity declined less strongly over time in ALS patients treated with PEA than in untreated patients. The oocyte findings are preclinical; the clinical statement rests on an observation without randomised control and without a stated case number in the excerpt. Whether the smaller decline in vital capacity withstands controlled testing remains open.

Overall Picture

Across the fields, randomised, placebo-controlled studies with pain and function scales in knee osteoarthritis, diabetic neuropathy and chronic pain, studies on schizophrenia and on olfactory dysfunction after COVID-19 with PEA and luteolin as well as meta-analyses summarising 774 and 933 patients respectively contribute^{6 12}. The pooled estimate of a standardised mean difference of 1.68 (95 % CI 1.05 to 2.31) and the superiority over control ($p < 0.00001$) at 933 patients are the most broadly supported figures; both are qualified by the authors themselves, in one case by the joint administration of placebo and active comparators, in the other by heterogeneity of $I^2 = 99\%$ with indication of publication bias. At the level of individual randomised studies, osteoarthritis, diabetic neuropathy and negative symptoms of schizophrenia stand with significant results, while the mechanistic study in 14 healthy volunteers altered experimental pain measures but did not examine clinical endpoints.

Where combinations were tested, the contribution of PEA alone cannot be read out: PEA with luteolin in olfactory dysfunction after COVID-19, PEA with trans-polydatin in endometriosis and vestibulodynia, PEA in addition to duloxetine and pregabalin in fibromyalgia, ultramicronised PEA in addition to interferon- $\beta 1a$ in multiple sclerosis^{3 9 36 37 4}. Several works are open-label, several report only the end time point. Research on tumour-associated pain begins at the start: the only evaluated work on older pain patients explicitly excluded cancer¹⁶, and for influenza the findings from six studies of the previous century are available, summarised in a 2013 review³³. What remains to be clarified is whether PEA is tested in tumour-related pain and which formulation prevails in direct comparison.

Methodology

The evaluated works comprise randomised double-blind placebo-controlled studies, a crossover study in healthy volunteers, blinded N-of-1 trials, open controlled studies, prospective and retrospective observations, a case series, a case-control study as well as systematic reviews and meta-analyses. Treatment durations range from four and eight weeks as well as 60 days up to six months and one year; in addition, a submaximal isometric exercise over three minutes was examined. Endpoints are predominantly pain and function scales (NRS, VAS, WOMAC, BPI-DPN, NPSI), alongside sleep, mood and symptom scales (PSQI, MOS, DASS-21, PANSS, EDSS) as well as laboratory and function measures (interleukin-6, C-reactive protein, intraocular pressure, visual field, forced vital capacity, Sniffin' Sticks). Direct comparisons between unmicronised and micronised formulations, information on data dispersion and reports on time points outside the final measurement remain to be seen.

Overall Picture

Combination preparations obscure the single substance

The thesis: The study situation on PEA supports pain, not the breadth of application areas. The compilation shows many controlled works, yet they are distributed across inflammation, metabolism, cognition, immune system, oncology, antiviral questions and bone. In most of these fields a single work or only a few stand. Whoever infers a tested effect in an application area from the existence of a study overextends it. A randomised work in healthy volunteers shows no effect in patients, and a questionnaire value is not a disease course.

The second point concerns the

COMBINATIONS

. Several frequently cited works test PEA together with luteolin, with trans-polydatin or with cannabidiol, another as an add-on to an antipsychotic. Such studies can show that an overall regimen is tolerable; they do not prove an effect of the single substance PEA. The same applies to the preparations: micronised and ultramicronised PEA are not the same preparation, and the works rarely compare them directly with each other. The open question is therefore not whether PEA occurs in studies, but which statement remains when combination studies and preliminary works are subtracted.

3. How Reliable the Research Is

Research on PEA is predominantly **clinical**: controlled studies in humans form the largest block; alongside stand observational studies, mechanistic reviews and animal experimental works. By application area, **inflammation** and **tolerability** dominate, followed by **metabolism**, **cognition**, **musculoskeletal system** and **fatigue**. Smaller fields are immune system, oncology, antiviral questions and bone. The common thread runs through **pain**: neuropathic, nociceptive and musculoskeletal pain, carpal tunnel syndrome, sciatic pain, endometriosis-related pain, knee osteoarthritis and burning-mouth syndrome. A second strand concerns inflammatory accompanying situations such as side effects of interferon therapy or the intestinal barrier. The breadth of application areas exceeds the number of works per area.

PROVEN Systematic reviews and meta-analyses of double-blind randomised studies exist for chronic pain; this is the most reliable level this field reaches, and the direction of the results is not yet stated. **Plausible**: For individual indications such as knee osteoarthritis or burning-mouth syndrome the statement rests on single randomised studies, partly marked as preliminary. **Hypothesis**: The animal experimental findings on neuroinflammation and intestinal barrier describe **preclinical** mechanisms; whether they map to humans is open. Methodologically it is noticeable that several controlled works were open-label and that studies in healthy volunteers pose different questions than studies in patients. What remains to be clarified is which preparation and which endpoint would make the studies comparable.

4. What Is Frequently Claimed — and What the Data Provide

STATEMENT	STUDY SITUATION
Chronic pain	Systematic reviews and meta-analyses of double-blind randomised studies are available here, representing the most robust level in this field. The direction of
Knee osteoarthritis	A double-blind, placebo-controlled randomised study examined safety, tolerability and efficacy. It remains a single study; a summarising evaluation is still out
Schizophrenia	A randomised, double-blind, placebo-controlled study investigated PEA as an add-on to risperidone for negative symptoms. The adjuvant design does not all
Olfactory dysfunction after COVID-19	A randomised study compared olfactory training with a treatment consisting of PEA and luteolin; the publication is marked as preliminary. The combination and

5. Profile: Molecule and Charge

Palmitoylethanolamide (PEA) is not a single molecule, but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is exactly what the next section is about.

6. Charge, Electrons, Radicals

PEA has no radical-scavenging activity, unlike polydatin (PLD), a natural precursor of resveratrol ²⁷. Measured were the secretion of tumour necrosis factor alpha and the formation of reactive oxygen species by stimulated macrophages in plasma as well as the cholesterol efflux capacity of the plasma ²⁵. Hypothesis: The reduction of reactive oxygen species could occur via signalling pathways and not via a direct radical reaction.

The evidence contains no measurements on charge, cation exchange and electron transfer; whether PEA acts there would need to be examined. Signalling pathways in human tissue were investigated: antagonists at CB1, CB2, TRPV1 and PPAR as well as inhibitors of PKA, nitric oxide synthase, phosphoinositide 3-kinases, MEK/ERK, adenylyl cyclase and protein kinase C were used ²⁶. The effects of PEA and CBD were abolished by inhibition of PKA, MEK/ERK and adenylyl cyclase (P < 0.001) ²⁶. Whether this reduction is coupled to one of the mentioned kinases would be the next examination step.

7. Interactions with Other Substances

With which other substances of the platform this substance is **jointly** investigated or discussed in human studies and review articles — combination, comparison or shared mechanism of action. The number indicates studies in which both occur.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
High-intensity interval training (HIIT)	349	249
Chronic inflammation	176	47
Red beet and nitrate	103	69
Vitamin D	87	7

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Breathing therapy and breathwork	69	35
Stress, cortisol and inflammation	65	18
Caffeine	63	56
Gut microbiome	61	5
Melatonin	60	7
Functional electrical stimulation (FES)	59	21

No drug interactions or burdensome adverse effects have been described for PEA to date ⁸. PEA can be administered in addition to other analgesics without negative drug-drug interactions or used as a sole analgesic ²². As an endogenous fatty acid amide, a possible interaction with the endocannabinoid system is discussed ²⁹; a daily PEA formulation over 8 weeks versus placebo was tested in 103 adults ²⁹. Also investigated are a fixed combination of PEA and melatonin in migraine prophylaxis ³² as well as PEA together with CBT in PTSD ³¹. The available statements provide no information on absorption, CYP enzymes or plasma protein binding.

One point of connection is the sigma-1 receptor: haloperidol acts there as an antagonist ³⁰. For haloperidol there is only low-grade clinical evidence that it improves pain, combined with morphine, methadone or tramadol, in cancer, fibrosis, radiation necrosis or neuropathic pain ³⁰. PEA belongs to the endogenous bioactive lipids of the ALIAMides that modulate non-neuronal neuroinflammatory responses to neuropathic injury and systemic inflammation ³⁰, and modulates mast cell behaviour in acute and chronic inflammation ²⁸. It remains open whether a sigma-1-mediated interaction of PEA with opioids is measurable in humans.

8. Overdose, Tolerability, Limits

In controlled human studies with oral administration of palmitoylethanolamide (PEA) over one year, safety and tolerability were examined as secondary objectives; the authors report that um-PEA can be considered as add-on therapy for IFN-β1a-induced adverse effects ^{4 4}. In knee osteoarthritis no changes in clinical markers were observed, the product was well tolerated ⁵. In a study with 50 participants (25 per group) safety parameters were controlled and treated ¹³; the safety assessment showed no significant difference in extrapyramidal symptoms (ESRS) and the frequency of other complications between the PEA and placebo groups ($p > 0.05$) ¹³. In diabetic peripheral neuropathic pain the treatment was well tolerated, without changes in safety parameters ¹⁵.

In a further controlled human study, ocular toxicity and skin tolerability of CBD-, PEA- and hemp seed oil formulations were examined: in healthy participants no irritations or sensitisations occurred in the patch test ¹⁹; mild phototoxicity of a hemp seed oil product was observed after 48 hours compared with the negative control ¹⁹. The authors conclude that these specific formulations are not irritating and not sensitising in healthy adults, and suggest further research on long-term safety in dermatological diseases ¹⁹. The evidence provides no information on upper limits or contraindications; it remains open which dose ranges are considered safe beyond the tested periods and how tolerability presents with longer use and in dermatological diseases ¹⁹.

9. The Most Robust Studies

Ordered by strength of evidence, not by prominence. The complete evaluation includes significantly more studies; the most robust ones are presented here.

Controlled Studies in Humans

- ¹ Mechanisms of exercise-induced hypoalgesia (2014)
- ² Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy (2016)
- ³ Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with ... (2021)
- ⁴ Oral Palmitoylethanolamide Treatment Is Associated with Reduced Cutaneous Adverse Effects of Interferon-β1a and Circulating Proinflammatory Cytokines ... (2016)
- ⁵ A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee ... (2019)
- ⁶ Palmitoylethanolamide in the Treatment of Chronic Pain: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials (2023)
- ⁷ Ultra-micronized Palmitoylethanolamide Effects on Sleep-wake Rhythm and Neuropathic Pain Phenotypes in Patients with Carpal Tunnel Syndrome: An ... (2018)
- ⁸ Palmitoylethanolamide, a nutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome (2015)
- ⁹ Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis (2017)
- ¹⁰ The Effect of Palmitoylethanolamide on Pain Intensity, Central and Peripheral Sensitization, and Pain Modulation in Healthy Volunteers-A Randomized ... (2022)
- ¹¹ Efficacy of ultramicrosized palmitoylethanolamide in burning mouth syndrome-affected patients: a preliminary randomized double-blind controlled trial (2019)
- ¹² Effects of Palmitoylethanolamide (PEA) on Nociceptive, Musculoskeletal and Neuropathic Pain: Systematic Review and Meta-Analysis of Clinical Evidence (2022)

- ¹³ Adjuvant palmitoylethanolamide therapy with risperidone improves negative symptoms in patients with schizophrenia: A randomized, double-blinded ... (2022)
- ¹⁴ Role of palmitoylethanolamide (PEA) in depression: Translational evidence: Special Section on "Translational and Neuroscience Studies in Affective ... (2019)
- ¹⁵ A randomized controlled trial assessing the safety and efficacy of palmitoylethanolamide for treating diabetic-related peripheral neuropathic pain (2022)
- ¹⁶ N-of-1 Randomized Trials of Ultra-Micronized Palmitoylethanolamide in Older Patients with Chronic Pain (2017)
- ¹⁷ Effect of palmitoylethanolamide on visual field damage progression in normal tension glaucoma patients: results of an open-label six-month follow-up (2014)
- ¹⁸ Intrathecal morphine administration reduces postoperative pain and peripheral endocannabinoid levels in total knee arthroplasty patients: a ... (2018)
- ¹⁹ Tolerability profile of topical cannabidiol and palmitoylethanolamide: a compilation of single-centre randomized evaluator-blinded clinical and in ... (2021)
- ²⁰ Efficacy and safety of palmitoylethanolamide as an adjunctive treatment for acute mania: A randomized, double-blind, placebo-controlled trial (2022)
- ²¹ Effectiveness of palmitoylethanolamide on endothelial dysfunction in ocular hypertensive patients: a randomized, placebo-controlled cross-over study (2013)
- ²² Chronic idiopathic axonal neuropathy and pain, treated with the endogenous lipid mediator palmitoylethanolamide: a case collection (2013)
- ²³ Micronized Palmitoylethanolamide: A Post Hoc Analysis of a Controlled Study in Patients with Low Back Pain - Sciatica (2019)
- ²⁴ Effects of Ultramicronized Palmitoylethanolamide (um-PEA) in COVID-19 Early Stages: A Case-Control Study (2022)

10. Summary

ESTABLISHED Systematic reviews and meta-analyses of double-blind randomised studies are available for chronic pain; the 2023 review included 11 studies with 774 patients and estimated the standardised mean difference at 1.68 (95% CI 1.05 to 2.31). Placebo and active comparators are jointly reported as comparators there, so the pooled figure does not show the distance to placebo alone. The 2016 review on safety and tolerability screened 16 clinical studies and states that the clinical data support an analgesic effect of PEA; for treatment durations up to 49 days, the data argue against serious adverse drug reactions from an incidence of 1/200.

PLAUSIBLE For knee osteoarthritis, the statement is based on individual randomised studies: In 111 adults, the WOMAC total score decreased under 300 mg ($p = 0.0372$) and 600 mg PEA ($p = 0.0012$) compared with placebo. For burning mouth syndrome, a preliminary randomised double-blind study showed a significant reduction in burning sensation under 600 mg ultramicronised PEA twice daily over 60 days ($p < 0.0132$). **Hypothesis:** That endogenous PEA fluctuates measurably during muscle work and under morphine suggests involvement in endogenous pain modulation; whether supplementation moves this regulatory circuit in the same direction has not been shown.

Direct comparisons of micronised and ultramicronised PEA are pending; in the combination studies with luteolin, trans-polydatin or cannabidiol, the single substance cannot be separated. It is also open whether the preclinical findings on neuroinflammation and intestinal barrier are reflected in humans. For the six clinical studies on influenza and colds with nearly 4000 people, a re-examination with current methods is pending.

11. What Remains Open

- **Preparation:** Which micronised or ultramicronised form and which dosing regimen would establish direct comparability of the studies has not been clarified.
- **Single Substance:** Studies that test PEA alone against PEA in combination would show what proportion of the findings is attributable to PEA.
- **Endpoints:** Whether changes in cytokines, questionnaires and sleep-wake rhythm are reflected in clinical courses is the crucial open question.

12. Further Paths

Topics, mechanisms of action and chains in which this substance occurs — for all those who want to look beyond the substance.

- Interaction Network

Frequently Asked Questions

Why do the studies distinguish between micronised and ultramicronised PEA?

The works use different degrees of grinding. **Hypothesis:** A finer preparation is better absorbed. A direct comparison of the preparations in humans is still pending. For the assessment this means that two studies with different preparations cannot be readily placed side by side and that a statement about the actually absorbed amount does not follow from this.

How has tolerability been investigated?

Safety and tolerability form, alongside inflammation, the largest application area of the controlled studies. They were recorded, among other things, in placebo-controlled works on knee osteoarthritis and on pain patterns as well as in the pharmacokinetic overview on pain treatment. These works list tolerability as a separate endpoint; this page does not reproduce concrete frequencies.

Is there a direct comparison with a pain medication?

Yes, a frequently cited controlled work from 2012 compared PEA with a non-steroidal anti-rheumatic drug in inflammatory pain of the temporomandibular joint. The title does not state the result; the existence of the comparison does not imply equivalence. Such head-to-head works are the most informative form for locating PEA in relation to an established treatment, and in the recorded material it is essentially this one.

Sources

- 1 Mechanisms of exercise-induced hypoalgesia
Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C · 2014
- 2 Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy
Gabrielsson L, Mattsson S, Fowler CJ · 2016
- 3 Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results
D'Ascanio L, Vitelli F, Cingolani C, Maranzano M, Brenner MJ, Di Stadio A · 2021
- 4 Oral Palmitoylethanolamide Treatment Is Associated with Reduced Cutaneous Adverse Effects of Interferon- β 1a and Circulating Proinflammatory Cytokines in Relapsing-Remitting Multiple Sclerosis
Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A et al. · 2016
- 5 A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis
Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L · 2019
- 6 Palmitoylethanolamide in the Treatment of Chronic Pain: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials
Lang-Ilievich K, Klivinyi C, Lasser C, Brenna CTA, Szilagyi IS, Bornemann-Cimenti H · 2023
- 7 Ultra-micronized Palmitoylethanolamide Effects on Sleep-wake Rhythm and Neuropathic Pain Phenotypes in Patients with Carpal Tunnel Syndrome: An Open-label, Randomized Controlled Study
Evangelista M, Cilli, De Vitis R, Militerno A, Fanfani F · 2018
- 8 Palmitoylethanolamide, a nutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome
Keppel Hesselink JM, Kopsky DJ · 2015
- 9 Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis
Indraccolo U, Indraccolo SR, Mignini F · 2017
- 10 The Effect of Palmitoylethanolamide on Pain Intensity, Central and Peripheral Sensitization, and Pain Modulation in Healthy Volunteers-A Randomized, Double-Blinded, Placebo-Controlled Crossover Trial
Lang-Ilievich K, Klivinyi C, Rumpold-Seitlinger G, Dorn C, Bornemann-Cimenti H · 2022
- 11 Efficacy of ultramicrozoned palmitoylethanolamide in burning mouth syndrome-affected patients: a preliminary randomized double-blind controlled trial
Ottaviani G, Rupel K, Gobbo M, Poropat A, Zoi V, Faraon M et al. · 2019
- 12 Effects of Palmitoylethanolamide (PEA) on Nociceptive, Musculoskeletal and Neuropathic Pain: Systematic Review and Meta-Analysis of Clinical Evidence
Scuteri D, Guida F, Boccella S, Palazzo E, Maione S, Rodríguez-Landa JF et al. · 2022
- 13 Adjuvant palmitoylethanolamide therapy with risperidone improves negative symptoms in patients with schizophrenia: A randomized, double-blinded, placebo-controlled trial
Salehi A, Namaei P, TaghaviZanjani F, Bagheri S, Moradi K, Khodaei Ardakani MR et al. · 2022
- 14 Role of palmitoylethanolamide (PEA) in depression: Translational evidence: Special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders
De Gregorio D, Manchia M, Carpinello B, Valtorta F, Nobile M, Gobbi G et al. · 2019
- 15 A randomized controlled trial assessing the safety and efficacy of palmitoylethanolamide for treating diabetic-related peripheral neuropathic pain
Pickering E, Steels EL, Steadman KJ, Rao A, Vitetta L · 2022
- 16 N-of-1 Randomized Trials of Ultra-Micronized Palmitoylethanolamide in Older Patients with Chronic Pain
Germini F, Coerezza A, Andreinetti L, Nobili A, Rossi PD, Mari D et al. · 2017
- 17 Effect of palmitoylethanolamide on visual field damage progression in normal tension glaucoma patients: results of an open-label six-month follow-up
Costagliola C, Romano MR, dell'Omo R, Russo A, Mastropasqua R, Semeraro F · 2014
- 18 Intrathecal morphine administration reduces postoperative pain and peripheral endocannabinoid levels in total knee arthroplasty patients: a randomized clinical trial
Kaczocha M, Azim S, Nicholson J, Rebecchi MJ, Lu Y, Feng T et al. · 2018
- 19 Tolerability profile of topical cannabidiol and palmitoylethanolamide: a compilation of single-centre randomized evaluator-blinded clinical and in vitro studies in normal skin
Maghfour J, Rietcheck H, Szetó MD, Rundle CW, Sivesind TE, Dellavalle RP et al. · 2021
- 20 Efficacy and safety of palmitoylethanolamide as an adjunctive treatment for acute mania: A randomized, double-blind, placebo-controlled trial
Abedini T, Hosseyni R, Ghannadi F, Moghaddam HS, Ardakani MK, Talaei A et al. · 2022
- 21 Effectiveness of palmitoylethanolamide on endothelial dysfunction in ocular hypertensive patients: a randomized, placebo-controlled cross-over study
Strobbe E, Cellini M, Campos EC · 2013
- 22 Chronic idiopathic axonal neuropathy and pain, treated with the endogenous lipid mediator palmitoylethanolamide: a case collection
Hesselink JM · 2013
- 23 Micronized Palmitoylethanolamide: A Post Hoc Analysis of a Controlled Study in Patients with Low Back Pain - Sciatica
Crucchi G, Stefano GD, Marchettini P, Truini A · 2019
- 24 Effects of Ultramicrozoned Palmitoylethanolamide (um-PEA) in COVID-19 Early Stages: A Case-Control Study
Albanese M, Marrone G, Paolino A, Di Lauro M, Di Daniele F, Chiaramonte C et al. · 2022
- 25 The secretion of tumor necrosis factor alpha and production of reactive oxygen species by stimulated macrophages incubat...
· 2024
- 26 Mechanisms were investigated using cannabinoid receptor 1 (CB1), cannabinoid receptor 2 (CB2), transient receptor potent...
· 2019
- 27 PEA lacks free radical scavenging activity, unlike polydatin (PLD), a natural precursor of resveratrol....
· 2016
- 28 PEA acts as an endogenous agent with an autacoid local inflammation antagonism and modulates mast cell behavior controll...
· 2012
- 29 Palmitoylethanolamide (PEA) is an endogenous fatty acid amide proposed to promote better sleep via potential interaction...
· 2021
- 30 Haloperidol is a sigma-1 receptor antagonist....
· 2024
- 31 Significant time $\times$ group interaction effects were observed ($p < 0,0001$), and no serious adverse events were reported....
· 2026
- 32 Fixed combination of palmitoylethanolamide and melatonin in preventive therapy of migraine: results from a randomized cl...
· 2025
- 33 Palmitoylethanolamide: A Natural Body-Owned Anti-Inflammatory Agent, Effective and Safe against Influenza and Common Cold
Keppel Hesselink JM, de Boer T, Witkamp RF · 2013
- 34 Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series
Hesselink JM, Hekker TA · 2012
- 35 Acetylcholine receptors from human muscle as pharmacological targets for ALS therapy
Palma E, Reyes-Ruiz JM, Lopergolo D, Roseti C, Bertolini C, Ruffolo G et al. · 2016
- 36 Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies
Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S · 2015
- 37 Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation
Murina F, Graziottin A, Felice R, Radici G, Tognocchi C · 2013
- 38 The Relationship of Endocannabinoid Lipid Mediators With Pain and Psychological Stress in Women With Fibromyalgia: A Case-Control Study
Stensson N, Ghafouri N, Ernberg M, Mannerkorpi K, Kosek E, Gerdle B et al. · 2018
- 39 Palmitoylethanolamide: A Natural Compound for Health Management
Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R · 2021
- 40 Palmitoylethanolamide: A Nutritional Approach to Keep Neuroinflammation within Physiological Boundaries-A Systematic Review
Petrosino S, Schiano Moriello A · 2020
- 41 Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A Review from Rodents to Humans
Landolfo E, Cutuli D, Petrosini L, Caltagirone C · 2022
- 42 Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR- α agonist and effective nutraceutical
Hesselink JM · 2013
- 43 Palmitoylethanolamide and Related ALIAMides for Small Animal Health: State of the Art
Della Rocca G, Re G · 2022

International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
ih-research.com/en/knowledge/palmitoylethanolamide/ · Last updated 2026-10-15