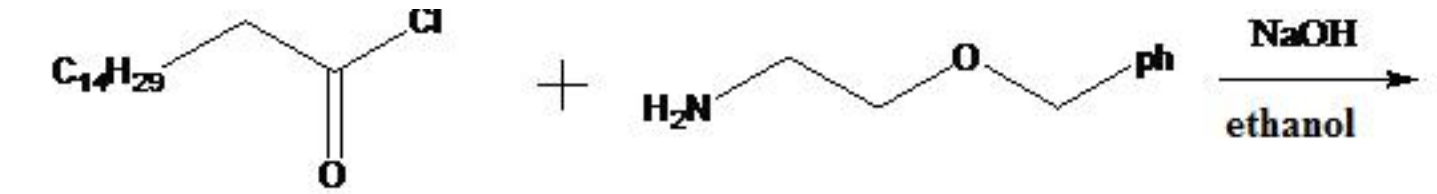
Palmitoylethanolamide (PEA)

Palmitoylethanolamide

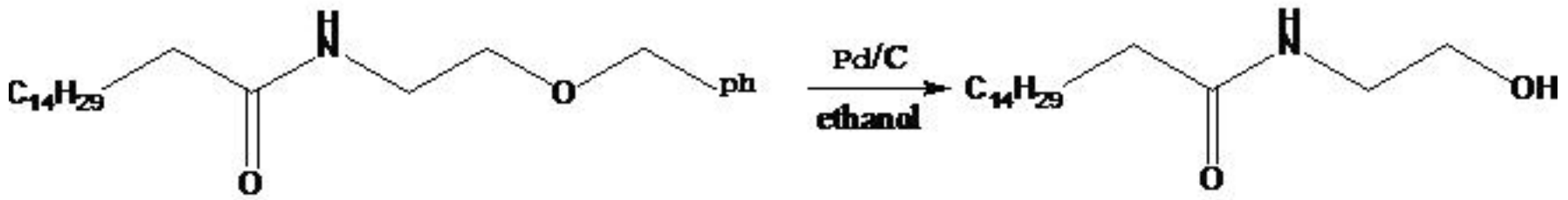
- **Palmitoylethanolamide** (**PEA**), a peroxisome proliferator-activated receptor alpha (PPAR-α) ligand that exerts anti-inflammatory, analgesic, and neuroprotective actions, for the treatment of neuro-inflammation, especially related to chronic pain, glaucoma and diabetic retinopathy.
  - The mechanism(s) of action of PEA involve its effects on the nuclear receptor PPARα (Gabrielsson et al., 2016).
  - It also involves mast cells, **cannabinoid receptor** type 2 (CB_2)-like cannabinoid receptors, ATP-sensitive potassium-channels, transient receptor potential (TRP) channels, and nuclear factor kappa B (NFkB).
  - It can affect endocannabinoid signaling by acting as a competing substrate for the endocannabinoid homologue anandamide (N-arachidonoylethanolamine).
- The initial observation was in 1943 by Coburn et al. as part of an epidemiological study focused on childhood rheumatic fever, the incidence of which was higher in those children consuming diets low in eggs.
  - These investigators noted that occurrence was reduced in children fed egg yolk powder, and subsequently they demonstrated anti-anaphylactic properties in guinea pigs with a lipid extract from egg yolk.
- 1957 Kuehl Jr. and coworkers reported to have succeeded in isolating a crystalline anti-inflammatory factor from soybean. They isolated the compound also from a phospholipid fraction of egg yolk and from hexane-extracted peanut meal.
  - Hydrolysis of PEA resulted in palmitic acid and ethanolamine and thus the compound was identified as *N*-(2-hydroxyethyl)-palmitamide (Kepple Hesselink et al., 2013).

Flow Chart of Semi-synthesize Palmitoylethanolamide



Palmitoyl Chloride

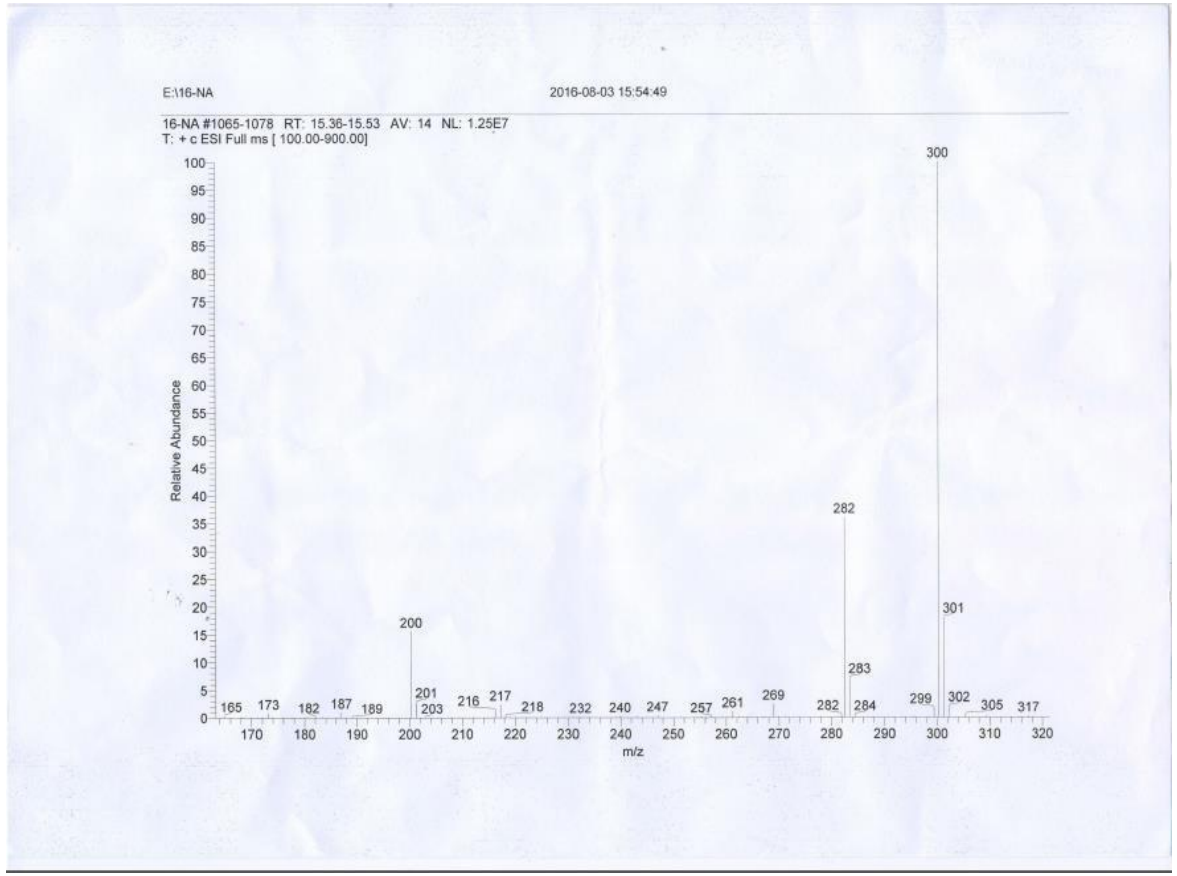
2-Aminoethyl Benzyl ether

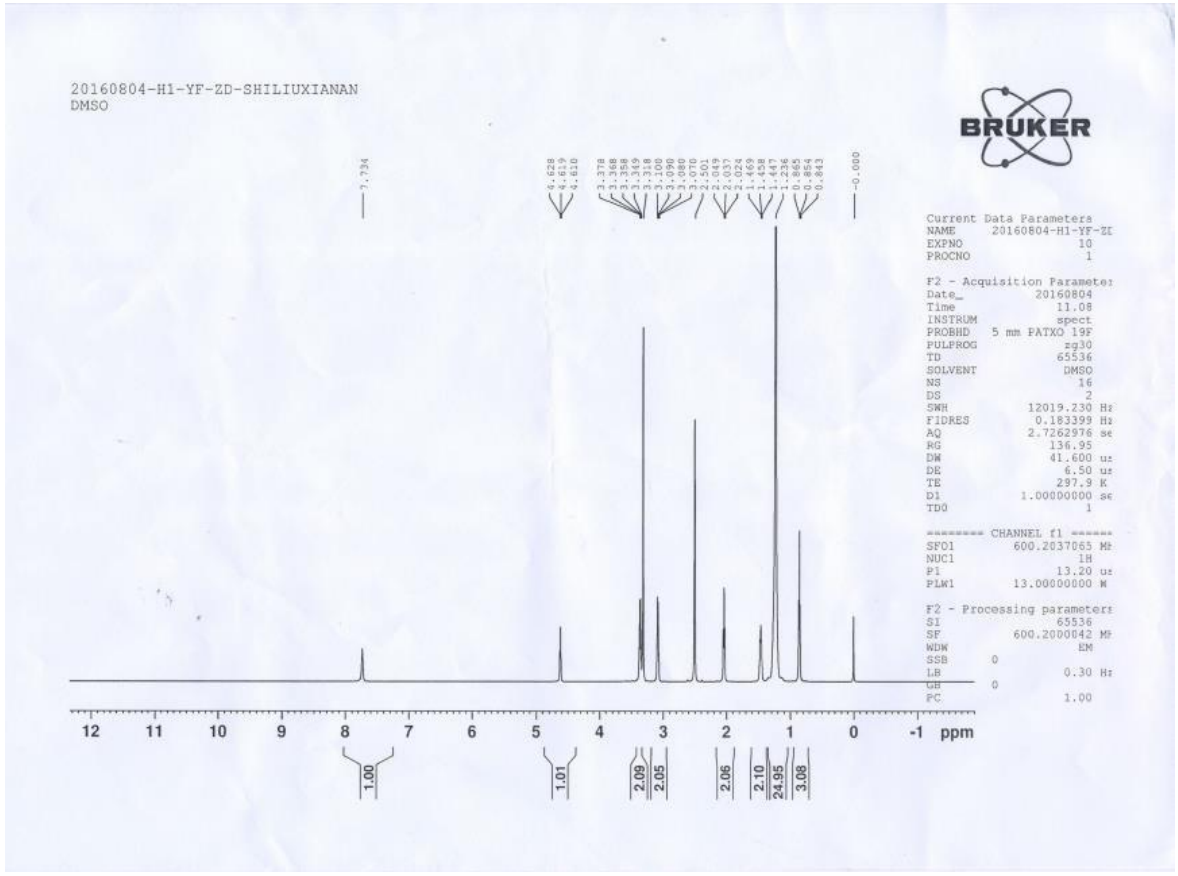


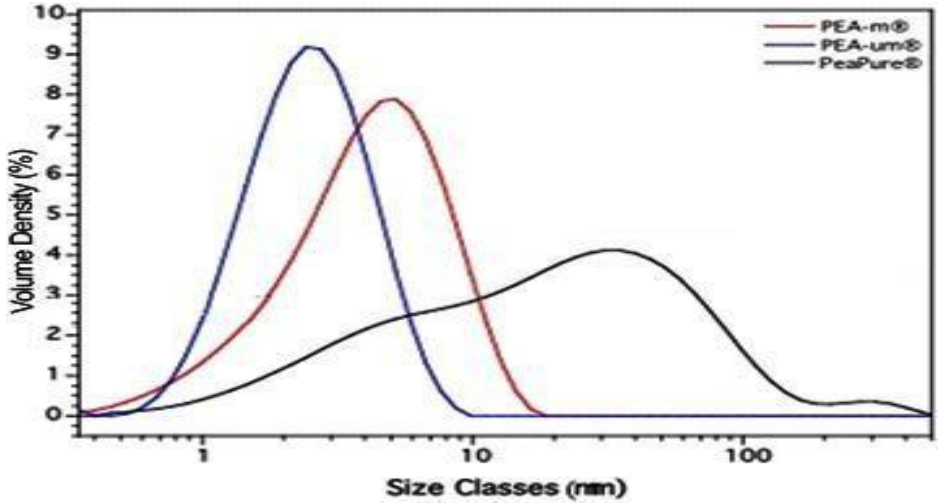
2-Benzyloxyethyl Hexadecanamide

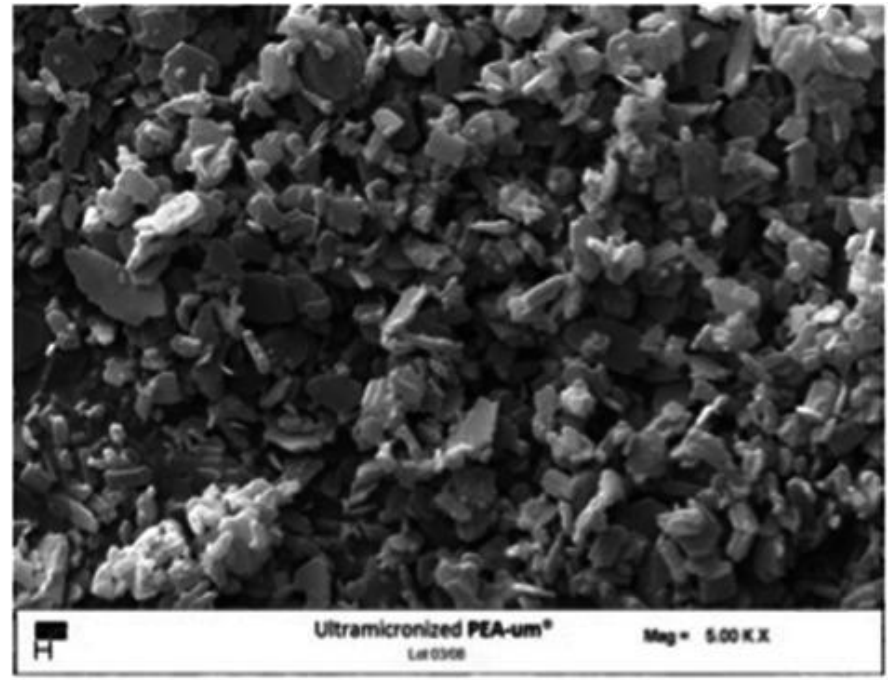
N- Palmitoylethanolamide

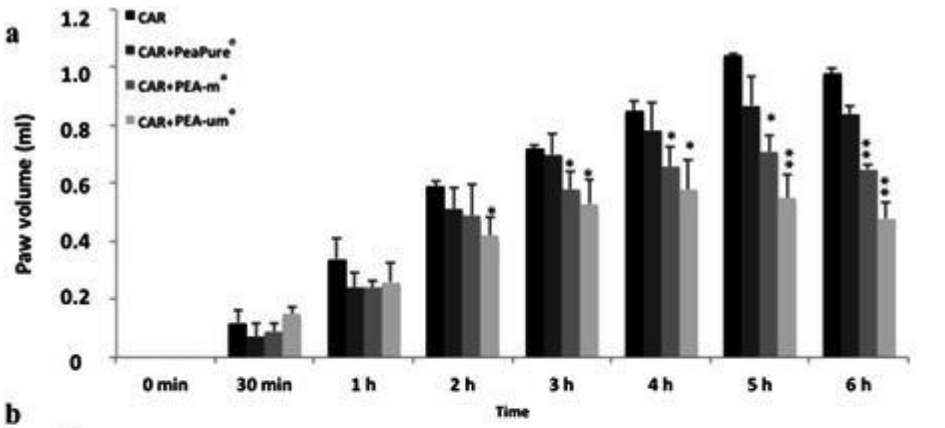
Mass Spectra (ESI-MS: m/z 300($M+H^+$) and Nuclear Magnetic Resonance (NMR) of PEA






PEA-m®
PEA-um®
PeaPure®
Volume Density (%)
Size Classes (nm)


Ultramicronized PEA-um®
Mag = 5.00 K X


a
CAR
CAR+PeaPure®
CAR+PEA-m®
CAR+PEA-um®
Paw volume (ml)
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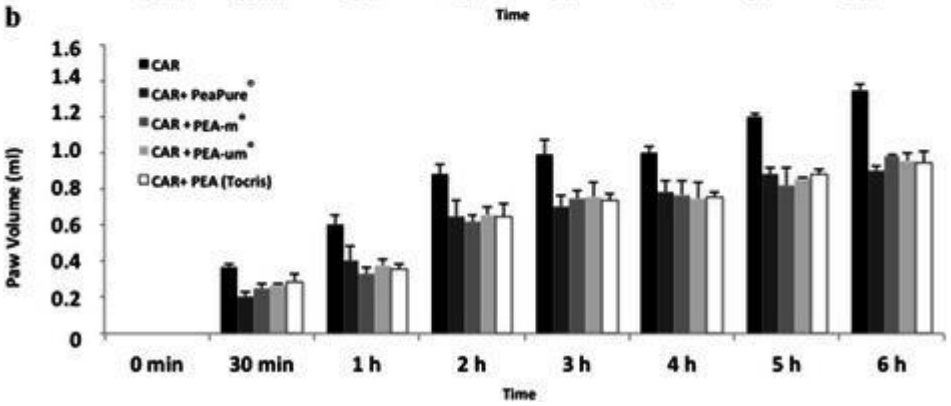
b
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CAR+ PeaPure®
CAR + PEA-m®
CAR + PEA-um®
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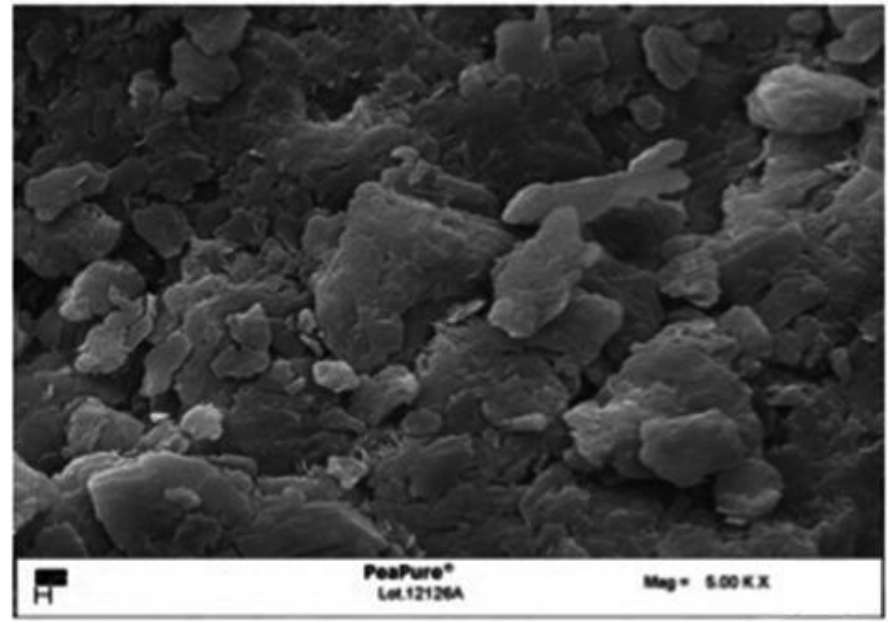

PeaPure®
Mag = 5.00 K X

Food Science & Nutrition DOI 10.1002/fsn3.392

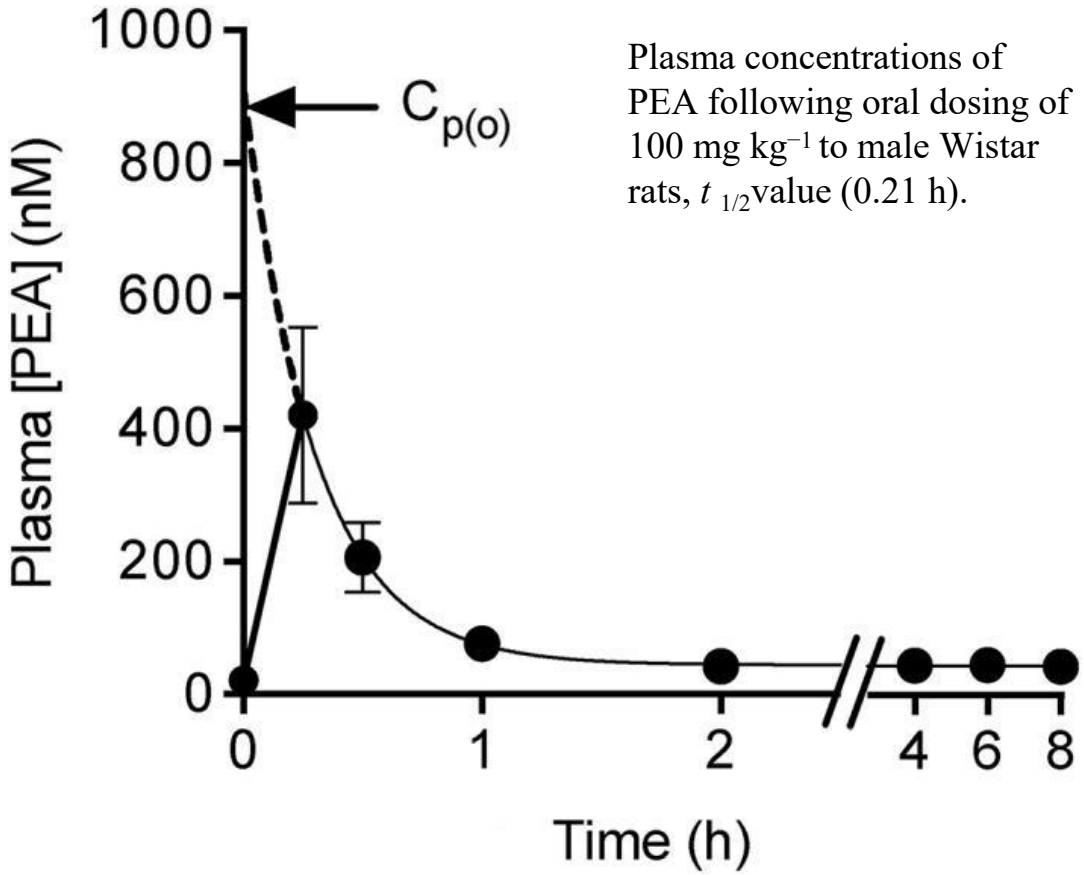
Safety of micronized palmitoylethanolamide (microPEA): lack of toxicity and genotoxic potential

- Palmitoylethanolamide (PEA) is a natural fatty acid amide found in a variety of foods, which was initially identified in egg yolk.
- MicroPEA of defined particle size (0.5–10 μm) was evaluated for mutagenicity in *Salmonella typhimurium,* for clastogenicity/aneuploidy in cultured human lymphocytes, and for acute and subchronic rodent toxicity in the rat, following standard OECD test protocols, in accordance with Good Laboratory Practice (GLP).
- PEA did not induce mutations in the bacterial assay using strains TA1535, TA97a, TA98, TA100, and TA102, with or without metabolic activation, in either the plate incorporation or liquid preincubation methods. Similarly, PEA did not induce genotoxic effects in human cells treated for 3 or 24 h without metabolic activation, or for 3 h with metabolic activation.
- PEA was found to have an LD50 greater than the limit dose of 2000 mg/kg body weight (bw), using the OECD Acute Oral Up and Down Procedure. Doses for the 90-day rat oral toxicity study were based on results from the preliminary 14-day study, that is, 250, 500, and 1000 mg/kg bw/day.
- The No Effect Level (NOEL) in both subchronic studies was the highest dose tested.

Br J Clin Pharmacol. 2016 Oct;82(4):932-42.

Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy

- Sixteen clinical trials, six case reports/pilot studies and a meta-analysis of PEA as an analgesic have been published in the literature.
  - For treatment times up to 49 days, the current clinical data argue against serious adverse drug reactions (ADRs) at an incidence of 1/200 or greater.
  - For treatment lasting more than 60 days, the number of patients is insufficient to rule out a frequency of ADRs of less than 1/100.
- The six published randomized clinical trials are of variable quality. Presentation of data without information on data spread and nonreporting of data at times other than the final measurement were among issues that were identified.
- Further, there are no head-to-head clinical comparisons of unmicronized vs. micronized formulations of PEA, and so evidence for superiority of one formulation over the other is currently lacking.
- Nevertheless, the available clinical data support the contention that PEA has analgesic actions and motivate further study of this compound, particularly with respect to head-to-head comparisons of unmicronized vs. micronized formulations of PEA and comparisons with currently recommended treatments.



Plasma concentrations of PEA following oral dosing of 100 mg kg^{-1} to male Wistar rats, $t_{1/2}$ value (0.21 h).

Clinical evidences

- Special Food for Medical Purposes, in the Treatment of Chronic Pain
- Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients
- Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome
- Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies
- Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease.
- Chronic pelvic pain, quality of life and sexual health of women treated with palmitoylethanolamide and α-lipoic acid
- Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome.
- Co-ultramicronized Palmitoylethanolamide/Luteolin in the Treatment of Cerebral Ischemia: from Rodent to Man
- Palmitoylethanolamide, a Natural Retinoprotectant: Its Putative Relevance for the Treatment of Glaucoma and Diabetic Retinopathy
- N-palmitoylethanolamine and N-acetylethanolamine are effective in asteatotic eczema: results of a randomized, double-blind, controlled study in 60 patients

Rheumatic pains:

Rheumatic arthritis
Bechterew's syndrome
Osteoarthritis

Neuropathic pain syndromes:

Pain after chemotherapy
Diabetic pains
Shingles
Pain due to MS
Pain due to CIAP

Nerve entrapment pains:

Carpal tunnel syndrome
Tarsal tunnel syndrome
Perineal nerve pain
Hernia
Sciatica

Palmitoylethanolamide
Circle of pain indications

Pelvic pain syndromes:

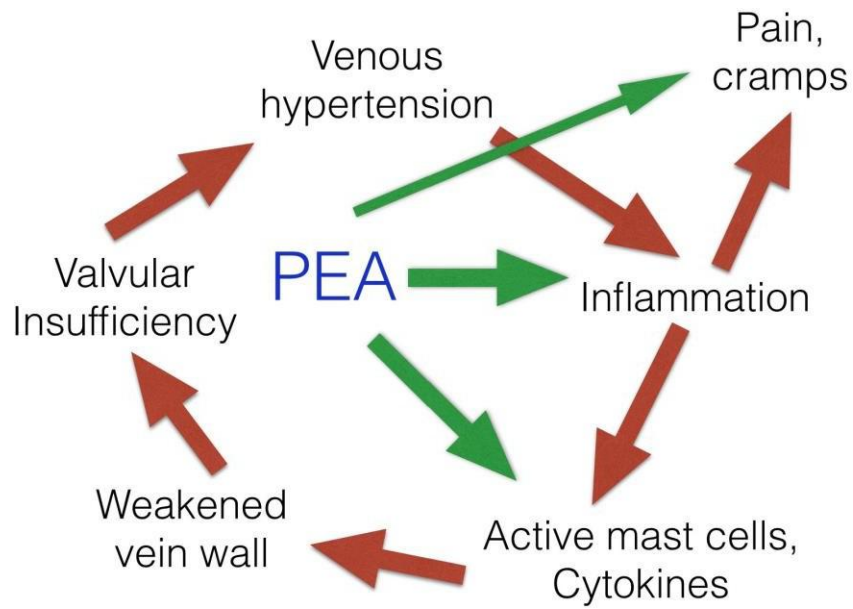
Vaginal pains and vulvodynia
Chronic prostate pains
Interstitial cystitis
Menstruation pains
Endometriosis

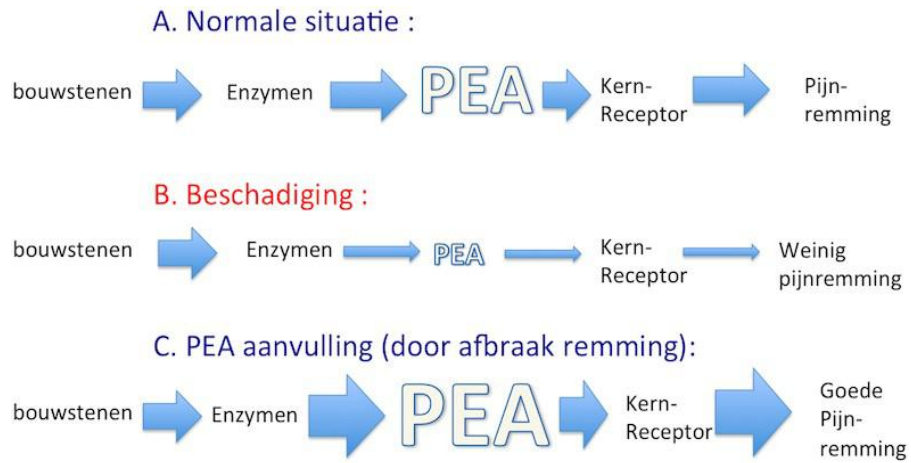
Inflammations:

Slow inflammation
Crohn's disease
Inflammatory Bowel Disease (IBD)
Common cold
Influenza

Chronic pain syndromes:

Irritable Bowel Syndrome (IBS)
Chronic widespread pain
Whiplash pains
Fibromyalgia





Naar professor Bradley K.Taylor, fysioloog, Pain 2013;154:326-327

Pijnstiller en Dosis in mg	Bij hoeveel patienten onderzocht	NNT
Etoricoxib 120	500	1.6
PEA 600	636	1.8
Celecoxib 400	298	2.1
Paracetamol 1000 + Codeine 60	197	2.2
Aspirin 1200	279	2.4
Ibuprofen 400	5456	2.5
Oxycodone IR 10 + Paracetamol 650	315	2.6
Ibuprofen 200	3248	2.7
Tramadol 150	561	2.9
Paracetamol 500	561	3.5
Ibuprofen 100	495	3.7
Paracetamol 1000	2759	3.8
Paracetamol 600/650 + Codeine 60	1123	4.2
Tramadol 100	882	4.8
Tramadol 75	563	5.3
Aspirin 650 + Codeine 60	598	5.3
Paracetamol 300 + Codeine 30	379	5.7

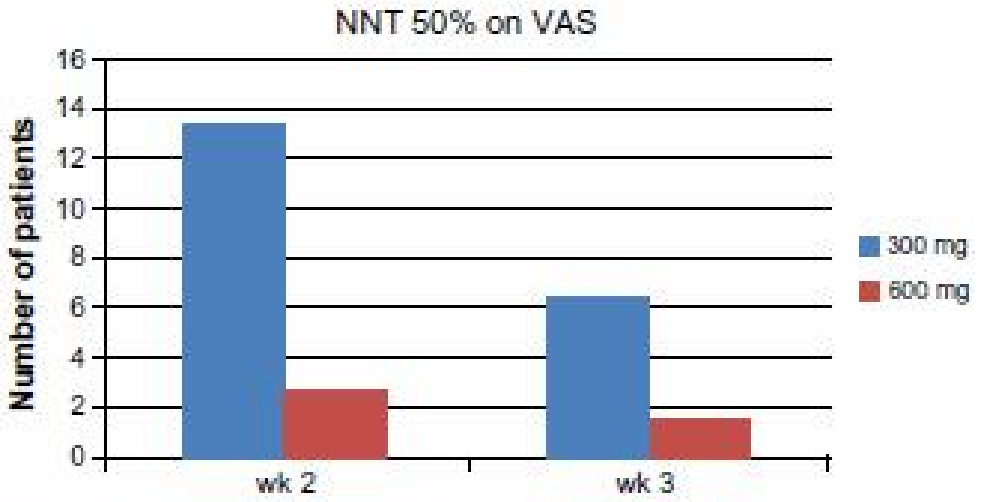
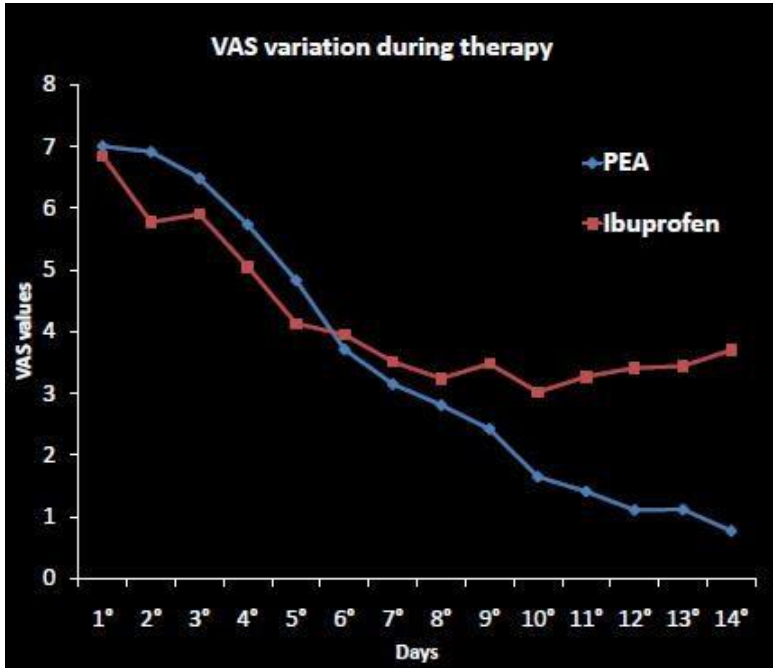


Figure 1 NNT of PEA to reach 50% reduction of pain.
Abbreviations: PEA, palmitoylethanolamide; VAS, visual analog scale; NNT, number needed to treat; wk, week.



Pain Physician. 2016 Feb;19(2):11-24.

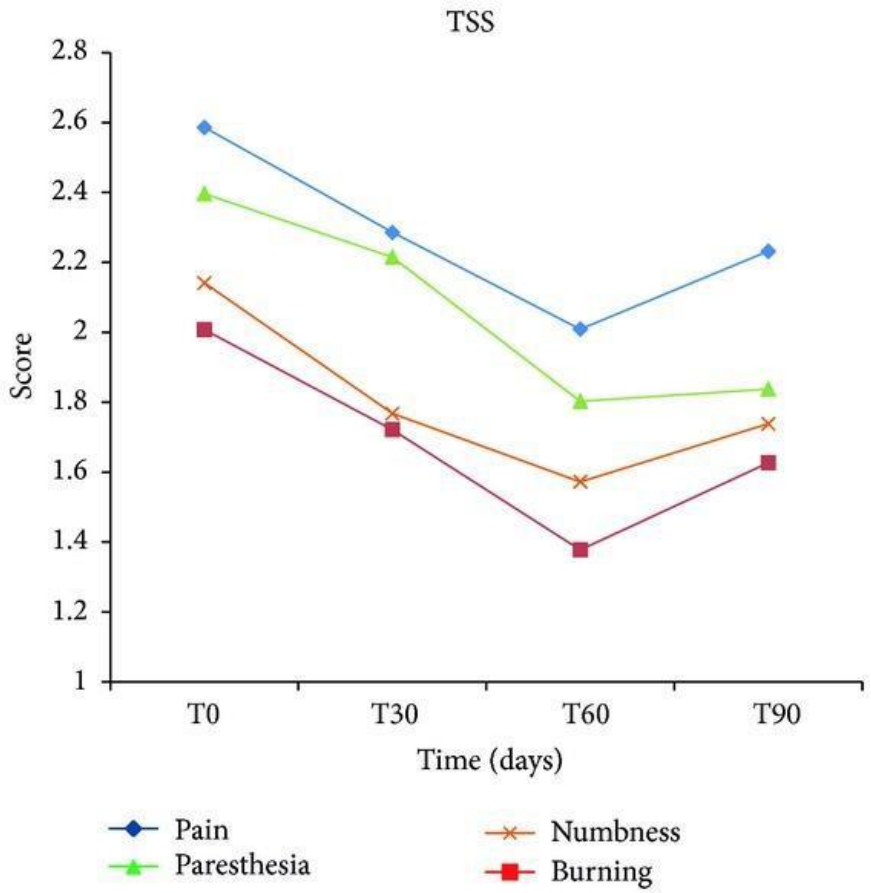
Palmitoylethanolamide, a Special Food for Medical Purposes, in the Treatment of Chronic Pain: A Pooled Data Meta-analysis.

- **BACKGROUND:** A growing body of evidence suggests that neuroinflammation, which is characterized by infiltration of immune cells, activation of mast cells and glial cells, and production of inflammatory mediators in the peripheral and central nervous systems, has an important role in the induction and maintenance of chronic pain. These findings support the notion that new therapeutic opportunities for chronic pain might be based on anti-inflammatory and pro-resolving mediators that act on immune cells, in particular mast cells and glia, to mitigate or abolish neuroinflammation. Among anti-inflammatory and pro-resolving lipid mediators, palmitoylethanolamide (PEA) has been reported to down-modulate mast cell activation and to control glial cell behaviors.
- **OBJECTIVE:** The aim of this study was to perform a pooled meta-analysis to evaluate the efficacy and safety of micronized and ultra-micronizedpalmitoylethanolamide (PEA) on pain intensity in patients suffering from chronic and/or neuropathic pain.
- **STUDY DESIGN:** Pooled data analysis consisting of double-blind, controlled, and open-label clinical trials.
- **METHODS:** Double-blind, controlled, and open-label clinical trials were selected consulting the PubMed, Google Scholar, and Cochrane databases, and proceedings of neuroscience meetings. The terms chronic pain, neuropathic pain, and micronized and ultra-micronized PEA were used for the search. Selection criteria included availability of raw data and comparability between tools used to diagnose and assess pain intensity. Raw data obtained by authors were pooled in one database and analyzed by the Generalized Linear Mixed Model. The changes in pain over time, measured by comparable tools, were also assessed by linear regression post-hoc analysis and the Kaplan-Meier estimate. Twelve studies were included in the pooled meta-analysis, 3 of which were double-blind trials comparing active comparators vs placebo, 2 were open-label trials vs standard therapies, and 7 were open-label trials without comparators.
- **RESULTS:** Results showed that PEA elicits a progressive reduction of pain intensity significantly higher than control. The magnitude of reduction equals 1.04 points every 2 weeks with a 35% response variance explained by the linear model. In contrast, in the control group pain, reduction intensity equals 0.20 points every 2 weeks with only 1% of the total variance explained by the regression. The Kaplan-Meier estimator showed a pain score = 3 in 81% of PEA treated patients compared to only 40.9% in control patients by day 60 of treatment. PEA effects were independent of patient age or gender, and not related to the type of chronic pain.
- **LIMITATIONS:** Noteworthy, serious adverse events related to PEA were not registered and/or reported in any of the studies.
- **CONCLUSION:** These results confirm that PEA might represent an exciting, new therapeutic strategy to manage chronic and neuropathic pain associated with neuroinflammation.

Pain Res Treat. 2014;2014:849623.

Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients.

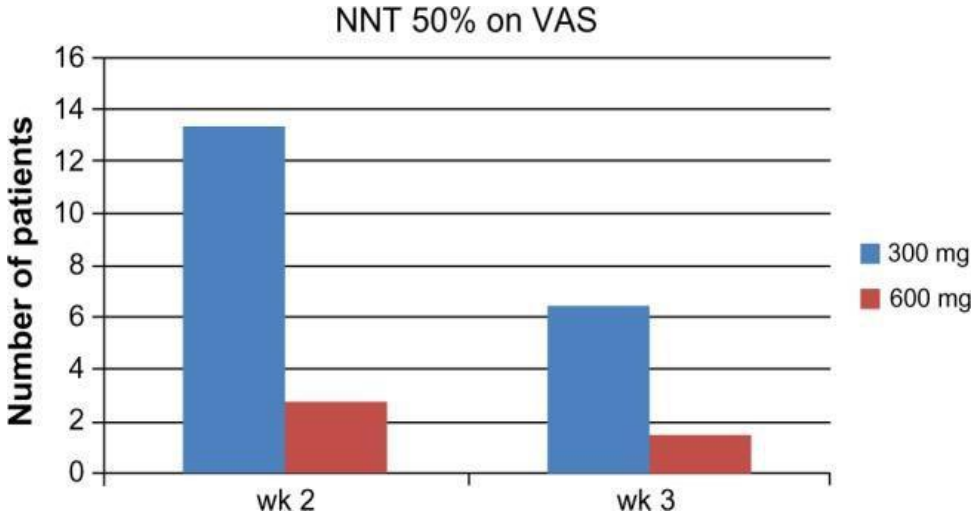
- The present study evaluated the effectiveness of micronized palmitoylethanolamide (PEA-m) treatment in reducing the painful symptoms experienced by diabetic patients with peripheral neuropathy.
  - PEA-m was administered (300 mg twice daily) to 30 diabetic patients suffering from painful diabetic neuropathy.
  - Before treatment start, after 30 and 60 days the following parameters were assessed: painful symptoms of diabetic peripheral neuropathy using the Michigan Neuropathy Screening instrument; intensity of symptoms characteristic of diabetic neuropathic pain by the Total Symptom Score; and intensity of different subcategories of neuropathic pain by the Neuropathic Pain Symptoms Inventory. Hematological and blood chemistry tests to evaluate metabolic control and safety were also performed.
  - Statistical analysis (ANOVA) indicated a highly significant reduction in pain severity ($P < 0.0001$) and related symptoms ($P < 0.0001$) evaluated by Michigan Neuropathy Screening instrument, Total Symptom Score, and Neuropathic Pain Symptoms Inventory.
  - Hematological and urine analyses did not reveal any alterations associated with PEA-m treatment, and no serious adverse events were reported.
- These results suggest that PEA-m could be considered as a promising and well-tolerated new treatment for symptomatology experienced by diabetic patients suffering from peripheral neuropathy.



J Pain Res. 2015 Oct 23;8:729-34.

Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome.

- Here we describe the results of all clinical trials evaluating PEA's efficacy and safety in nerve compression syndromes: sciatic pain and pain due to carpal tunnel syndrome, and review preclinical evidence in nerve impingement models.
  - In total, eight clinical trials have been published in such entrapment syndromes, and 1,366 patients have been included in these trials.
  - In one pivotal, double blind, placebo controlled trial in 636 sciatic pain patients, the number needed to treat to reach 50% pain reduction compared to baseline was 1.5 after 3 weeks of treatment.
  - PEA proved to be effective and safe in nerve compression syndromes, no drug interactions or troublesome side effects have been described.
- PEA should be considered as a new and safe treatment option for nerve compression syndromes.
  - Since the often prescribed co-analgesic pregabaline has been proven to be ineffective in sciatic pain in a double blind enrichment trial.
  - Physicians are not always aware of PEA as a relevant and safe alternative to opioids and co-analgesics in the treatment of neuropathic pain.

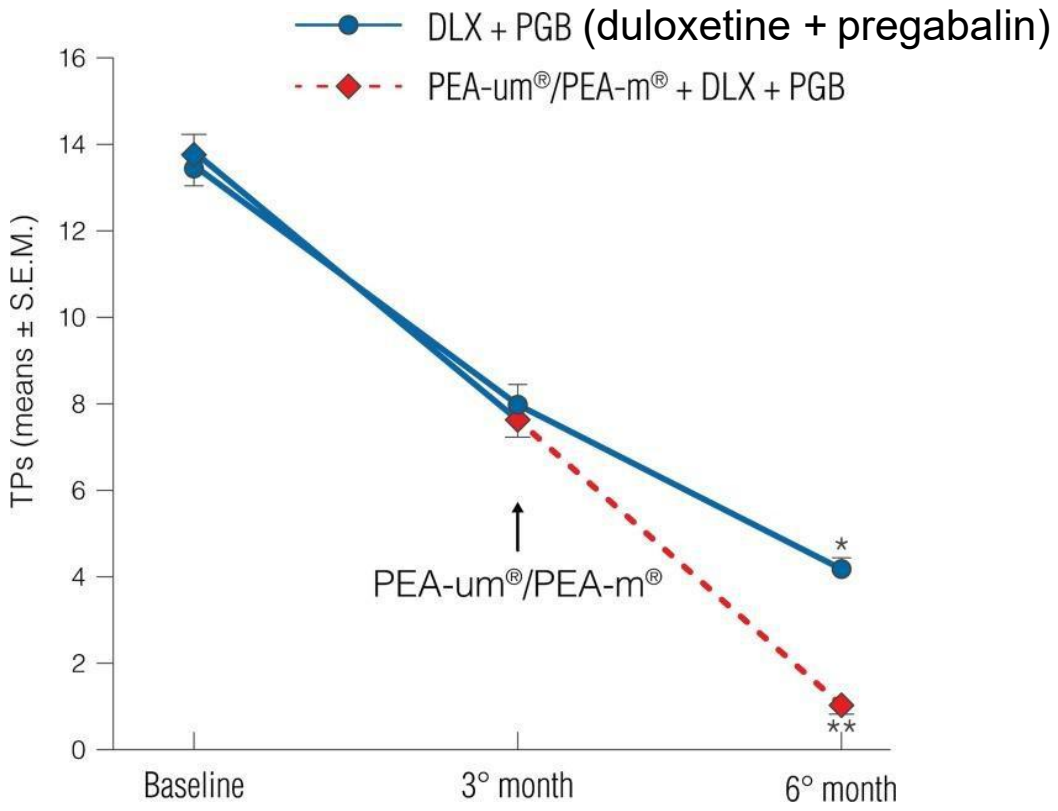


NNT of PEA to reach 50% reduction of pain

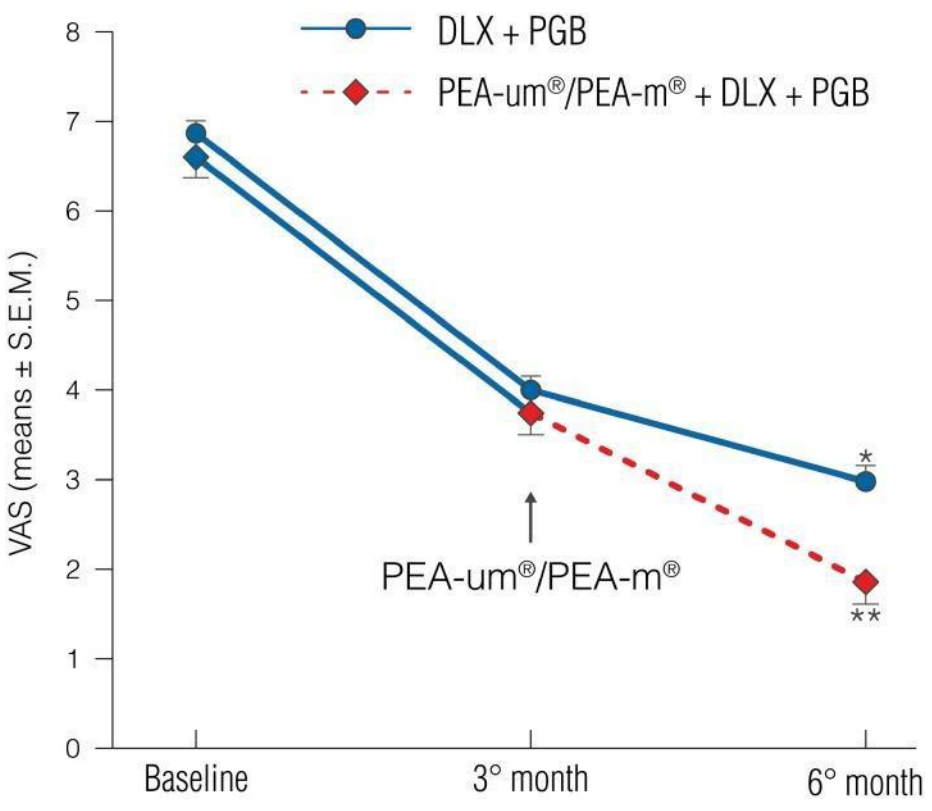
PEA, palmitoylethanolamide;
VAS, visual analog scale;
NNT, number needed to treat

Pain Ther. 2015 Dec;4(2):169-78.

Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies.



Reduction in number of positive tender points



Reduction in pain intensity by VAS measurement.

CNS Neurol Disord Drug Targets. 2017 Mar 21.

Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease.

BACKGROUND: Parkinson's disease (PD) is the subject of intense efforts to develop strategies that slow down or stop disease progression and disability. Substantial evidence points to a prominent role for neuroinflammation in the underlying dopaminergic cell death. Ultramicronized palmitoylethanolamide (um-PEA) is well-known for its ability to promote the resolution of neuroinflammation and exert neuroprotection. This study was designed to assess the efficacy of um-PEA as adjuvant therapy in patients with advanced PD.
METHODS: Thirty PD patients receiving levodopa were included in the study. The revise- Movement Disorder Society/Unified Parkinson's Disease Rating Scale (MDS-UPDRS) questionnaire was used to assess motor and non-motor symptoms. Clinical assessments were carried out before and after addition of um-PEA (600 mg). MDS-UPDRS questionnaire total score for parts I, II, III, and IV was analyzed using the Generalized Linear Mixed Model, followed by the Wilcoxon signed-rank test to evaluate the difference of each item's mean score between baseline and end of um-PEA treatment.
RESULTS: Addition of um-PEA to PD patients receiving levodopa therapy elicited a significant and progressive reduction in the total MDS-UPDRS score (parts I, II, III and IV). For each item, the mean score difference between baseline and end of um-PEA treatment showed a significant reduction in most non-motor and motor symptoms. The number of patients with symptoms at basal was reduced after one year of um-PEA treatment. None of the participants reported side effects attributable to the addition of um-PEA.
CONCLUSION: um-PEA slowed down disease progression and disability in PD patients, suggesting that um-PEA may be an efficacious adjuvant therapy for PD.

Minerva Ginecol. 2015 Oct;67(5):413-9.

Chronic pelvic pain, quality of life and sexual health of women treated with palmitoylethanolamide and α-lipoic acid.

- The aim of this paper was to evaluate the effects of the association between palmitoylethanolamide (PEA) and α-lipoic acid (LA) on quality of life (QoL) and sexual function in women affected by endometriosis-associated pelvic pain.
  - Fifty-six women constituted the study group and were given PEA 300 mg and LA 300mg twice daily.
  - To define the endometriosis-associated pelvic pain, the visual analogic scale (VAS) was used. The Short Form-36 (SF-36), the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) were used to assess the QoL, the sexual function and the sexual distress, respectively. The study included three follow-ups at 3, 6 and 9 months.
  - No changes were observed in pain, QoL and sexual function at the 3rd month follow-up (P=NS). By the 6th and 9th month, pain symptoms (P<0.001) and all categories of the QoL (P<0.001) improved. The FSFI and the FSDS scores did not change at the 3rd month follow-up (P=ns). On the contrary, at the 3rd and 9th months follow-ups they improved with respect to the baseline (P<0.001).
- The progressive reduction of the pain syndrome reported by women over the treatment period could contribute to improve the QoL and sexual life of women on PEA and LA.

Arch Ital Urol Androl. 2017 Mar 31;89(1):17-21.

The efficacy of an association of palmitoylethanolamide and alpha-lipoic acid in patients with chronic prostatitis/chronic pelvic pain syndrome: A randomizedclinical trial.

- **BACKGROUND:** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a complex condition, characterized by uncertain etiology and by limited response to therapy. The definition of CP/CPPS includes genitourinary pain with or without voiding symptoms in the absence of uropathogenic bacteria, as detected by standard microbiological methods, or another identifiable cause such as malignancy. The efficacy of various medical therapies, has been evaluated in clinical studies, but evidence is lacking or conflicting. We compared Serenoa Repens in monotherapy versus Palmitoylethanolamide (PEA) in combination with Alpha-lipoic acid (ALA) and evaluated the efficacy of these treatments in patients with CP/CPPS.
- **METHODS:** We conducted a randomized, single-blind trial. 44 patients diagnosed with CP/CPPS (mean age 41.32 ± 1.686 years) were randomly assigned to treatment with Palmitoylethanolamide 300 mg plus Alpha-lipoic acid 300 mg (Peanase®), or Serenoa Repens at 320 mg. Three questionnaires (NIH-CPSI, IPSS and IIEF5) were administered at baseline and after 12 weeks of treatment in each group.
- **RESULTS:** 12 week treatment with Peanase significantly improved the IPSS score compared to the same period of treatment with Serenoa Repens, and significantly reduced NIH-CPSI score. Similar results were observed in the different NIH-CPSI subscores break down. However, the same treatment did not result in significant improvement of the IIEF5 score. Both treatments did not produce undesired effects.
- **CONCLUSIONS:** The present results document the efficacy of an association of Palmitoylethanolamide (PEA) and Alpha-lipoic acid (ALA) administered for 12 weeks for treating patients with CP/CPPS, compared with Serenoa Repens monotherapy.

Aliment Pharmacol Ther. 2017 Feb 6.

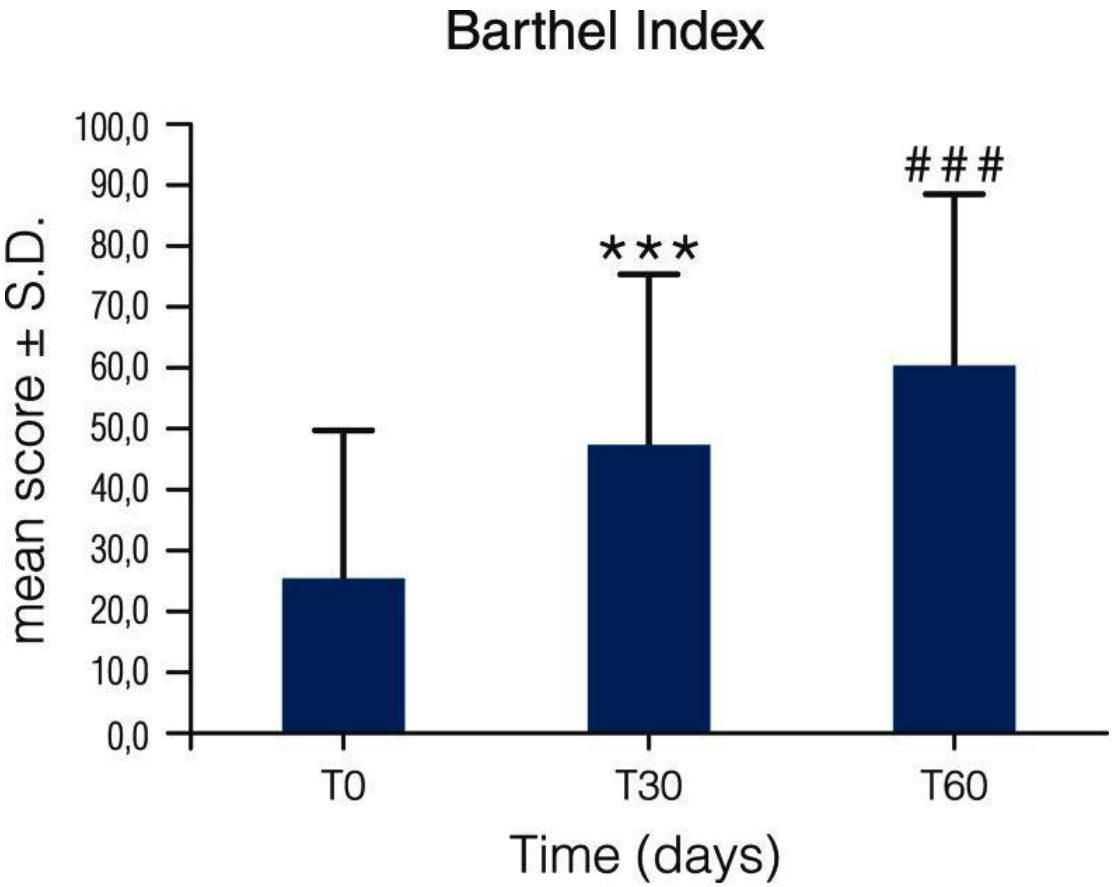
Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome.

- **BACKGROUND:** Intestinal immune activation is involved in irritable bowel syndrome (IBS) pathophysiology. While most dietary approaches in IBS involve food avoidance, there are fewer indications on food supplementation. Palmithoylethanolamide, structurally related to the endocannabinoid anandamide, and polydatin are dietary compounds which act synergistically to reduce mast cell activation.
- **AIM:** To assess the effect on mast cell count and the efficacy of palmithoylethanolamide/polydatin in patients with IBS.
- **METHODS:** We conducted a pilot, 12-week, randomised, double-blind, placebo-controlled, multicentre study assessing the effect of palmithoylethanolamide/polydatin 200 mg/20 mg or placebo b.d. on low-grade immune activation, endocannabinoid system and symptoms in IBS patients. Biopsy samples, obtained at screening visit and at the end of the study, were analysed by immunohistochemistry, enzyme-linked immunoassay, liquid chromatography and Western blot.
- **RESULTS:** A total of 54 patients with IBS and 12 healthy controls were enrolled from five European centres. Compared with controls, IBS patients showed higher mucosal mast cell counts (3.2 ± 1.3 vs. 5.3 ± 2.7%, P = 0.013), reduced fatty acid amide oleoylethanolamide (12.7 ± 9.8 vs. 45.8 ± 55.6 pmol/mg, P = 0.002) and increased expression of cannabinoid receptor 2 (0.7 ± 0.1 vs. 1.0 ± 0.8, P = 0.012). The treatment did not significantly modify IBS biological profile, including mast cell count. Compared with placebo, palmithoylethanolamide/polydatin markedly improved abdominal pain severity ($P < 0.05$).
- **CONCLUSIONS:** The marked effect of the dietary supplement palmithoylethanolamide/polydatin on abdominal pain in patients with IBS suggests that this is a promising natural approach for pain management in this condition. Further studies are now required to elucidate the mechanism of action of palmithoylethanolamide/polydatin in IBS. ClinicalTrials.gov number, NCT01370720.

Transl Stroke Res. 2016 Feb;7(1):54-69.

Co-ultramicronized Palmitoylethanolamide/Luteolin in the Treatment of Cerebral Ischemia: from Rodent to Man.

Patients were administered Glialia® for a period of 60 days.
Barthel Index values were 26.6 ± 1.69, 48.3 ± 1.91, and 60.5 ± 1.95 at T0 (242 patients), T30 (229 patients), and T60 (218 patients), respectively.
There was a significant difference in the improvement between T0 and T30 (***$p < 0.0001$) and between T0 and T60 ($^{###}p < 0.0001$). Moreover, there was a highly significant difference also between T30 and T60 ($p < 0.0001$).
Female patients exhibited lower scores than males, and disability was worse in inpatients



Drug Des Devel Ther. 2016 Sep 27;10:3133-3141.

Resolvins and aliamides: lipid autacoids in ophthalmology - what promise do they hold?

- Resolvins (Rvs) are a novel class of **lipid-derived endogenous molecules** (autacoids) with potent immunomodulating properties, which regulate the resolution phase of an active immune response.
  - These modulating factors are locally produced, influencing the function of cells and/or tissues, which are produced on demand and subsequently metabolized in the same cells and/or tissues.
- Autacoid pharmacology, developed in the 1970s, autacoid drugs are either the body-own compounds themselves or the precursors or other derivatives thereof, preferably based on simple chemistry, such as 5-hydroxytryptophan, a precursor for serotonin.
- The key function of autacoids belonging to these classes is to inhibit hyperactivated immune cascades and thus act like a "stop" signal in inflammation processes otherwise becoming pathological.
  - In 1993, the Nobel laureate Rita Levi-Montalcini (1909–2012) coined the term "aliamides" for such compounds, while working on the inhibiting and modulating role of palmitoylethanolamide (PEA) in overactive mast cells.
  - The concept of aliamides was derived from the acronym **ALIA: autacoid local inflammation antagonist**.
  - The term found its way into the field of *N*-acetylethanolamides autacoids, such as PEA, although "aliamide" was defined by Levi-Montalcini as a container concept for all lipid-inhibiting and -modulating mediators. That would also include the Rvs, protectins, and maresins.
- Rvs are metabolites of the polyunsaturated ω-3 fatty acids: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA).
  - The metabolites of EPA are termed E Rvs (RvEs), those of DHA are termed D Rvs (RvDs), and those of DPA are termed Rvs D ($RvDs_{n\text{-}3DPA}$) and Rvs T (RvTs).
  - Protectins and maresins are derived from the ω-3 fatty acid DHA.

J Ophthalmol. 2015;2015:430596.

Palmitoylethanolamide, a Natural Retinoprotectant: Its Putative Relevance for the Treatment of Glaucoma and Diabetic Retinopathy.

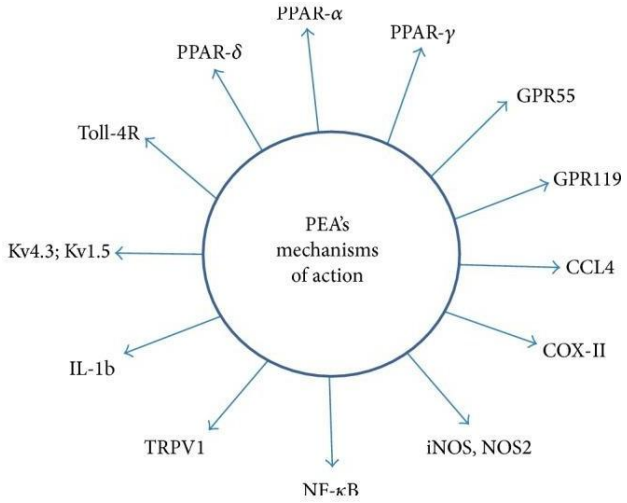
Retinopathy is a threat to the eyesight, and glaucoma and diabetes are the main causes for the damage of retinal cells. Recent insights pointed out a common pathogenetic pathway for both disorders, based on chronic inflammation.

PEA has been evaluated for glaucoma, diabetic retinopathy, and uveitis, pathological states based on chronic inflammation, respiratory disorders, and various pain syndromes in a number of clinical trials since the 70s of 20th century.

PEA has been tested in at least 9 double blind placebo controlled studies, among which two studies were in glaucoma, and found to be safe and effective up to 1.8 g/day, with excellent tolerability. PEA therefore holds a promise in the treatment of a number of retinopathies.

PEA is available as a food supplement (PeaPure) and as diet food for medical purposes in Italy (Normast, PeaVera, and Visimast).

These products are notified in Italy for the nutritional support in glaucoma and neuroinflammation. We discuss PEA as a putative anti-inflammatory and retinoprotectant compound in the treatment of retinopathies, especially related to glaucoma and diabetes.

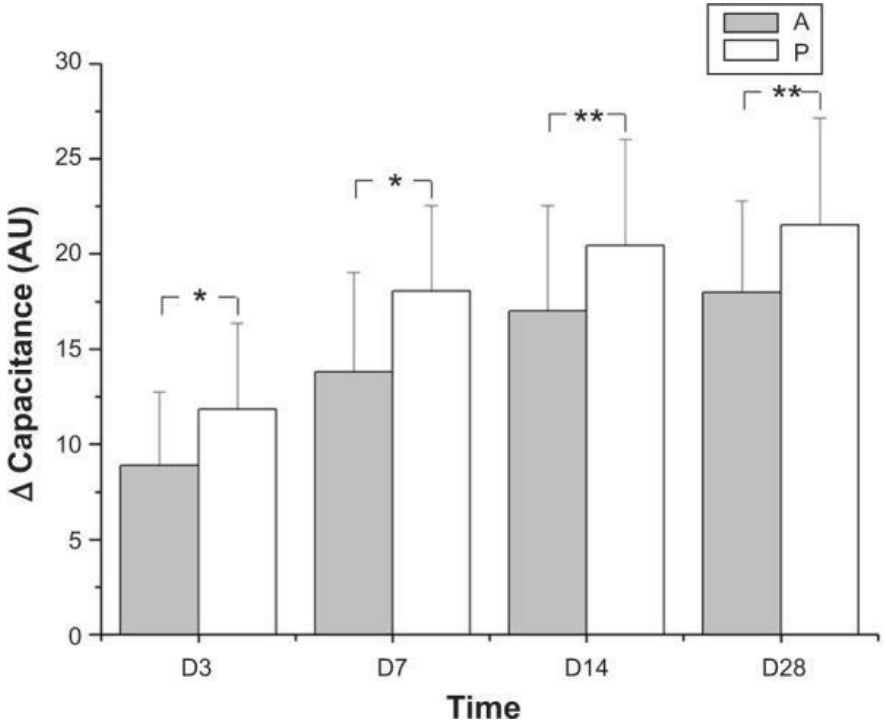


Different molecular targets of PEA. PPAR: peroxisome proliferator activated receptor; GPR-55: 119-orphan G-protein coupled receptors; CCL: chemokine ligand; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; TRPV: transient receptor potential cation channel subfamily V; IL: interleukin; Kv1.5,4.3: potassium voltage gated channels; Toll-4 R: toll-like receptor.

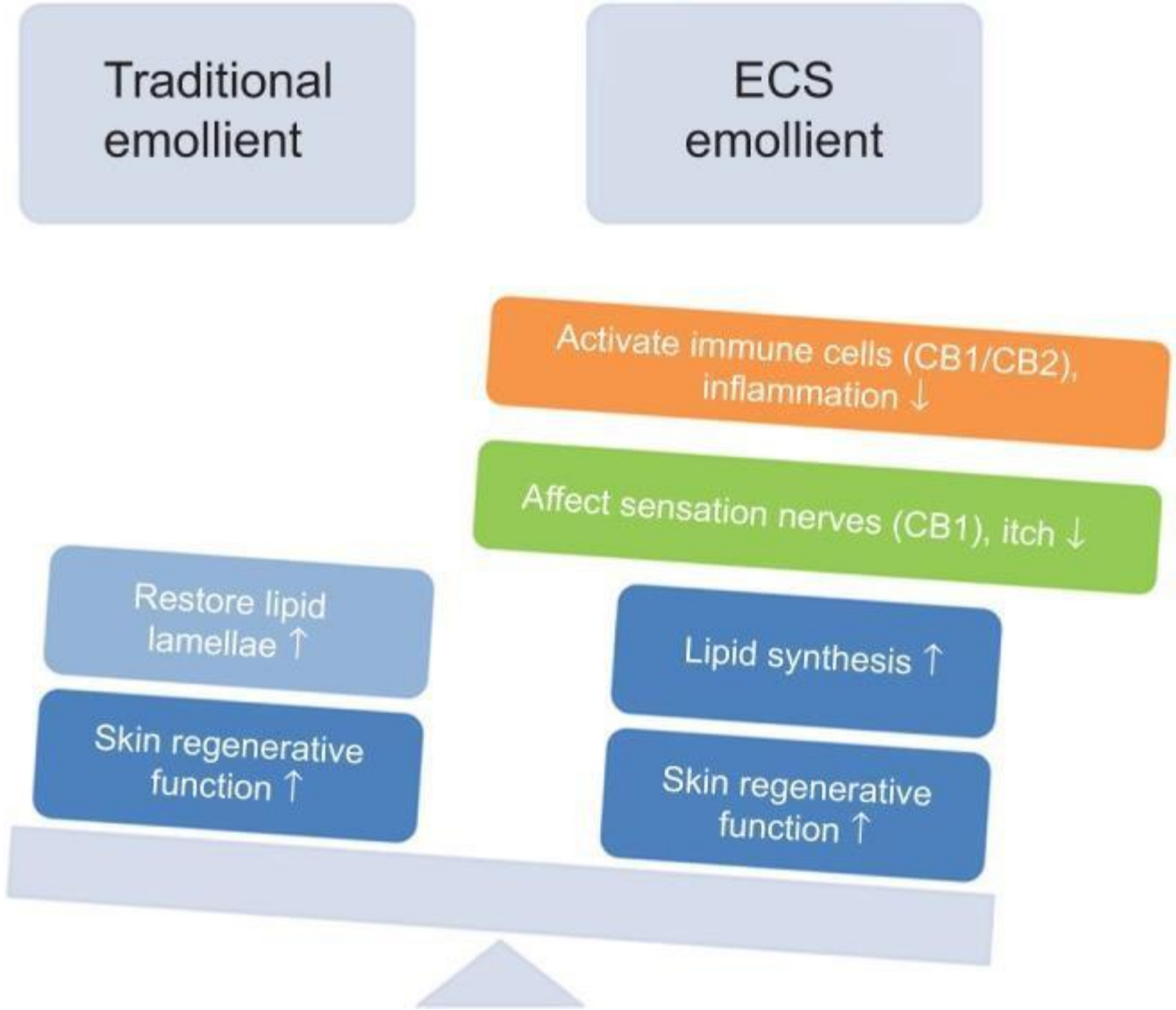
Clin Interv Aging. 2014 Jul 17;9:1163-9.

N-palmitoylethanolamine and N-acetylethanolamine are effective in asteatotic eczema: results of a randomized, double-blind, controlled study in 60 patients.

- **BACKGROUND:** Asteatotic eczema (AE) is characterized by itchy, dry, rough, and scaling skin. The treatments for AE are mainly emollients, usually containing urea, lactic acid, or a lactate salt. N-palmitoylethanolamine (PEA) and N-acetylethanolamine (AEA) are both endogenous lipids used as novel therapeutic tools in the treatment of many skin diseases. The purpose of this study was to compare a PEA/AEA emollient with a traditional emollient in the treatment of AE.
- **METHODS:** A monocentric, randomized, double-blind, comparative trial was conducted in 60 AE patients to evaluate and compare the efficacy of the two emollients. The level of skin dryness among the subjects ranged from mild to moderate. The subjects' skin barrier function and the current perception threshold were tested for 28 days by clinical scoring and bioengineering technology.
- **RESULTS:** The results showed that, although some aspects were improved in both groups, the group using the emollient containing PEA/AEA presented a better skin surface change in capacitance. However, the most impressive finding was the ability of the PEA/AEA emollient to increase the 5 Hz current perception threshold to a normal level after 7 days, with a significant difference between values at baseline and after 14 days. A current perception threshold of 5 Hz was positively and significantly correlated with skin surface hydration and negatively correlated with transepidermal water loss in the PEA/AEA emollient group.
- **CONCLUSION:** Compared with traditional emollients, regular application of a topical PEA/AEA emollient could improve both passive and active skin functions simultaneously.



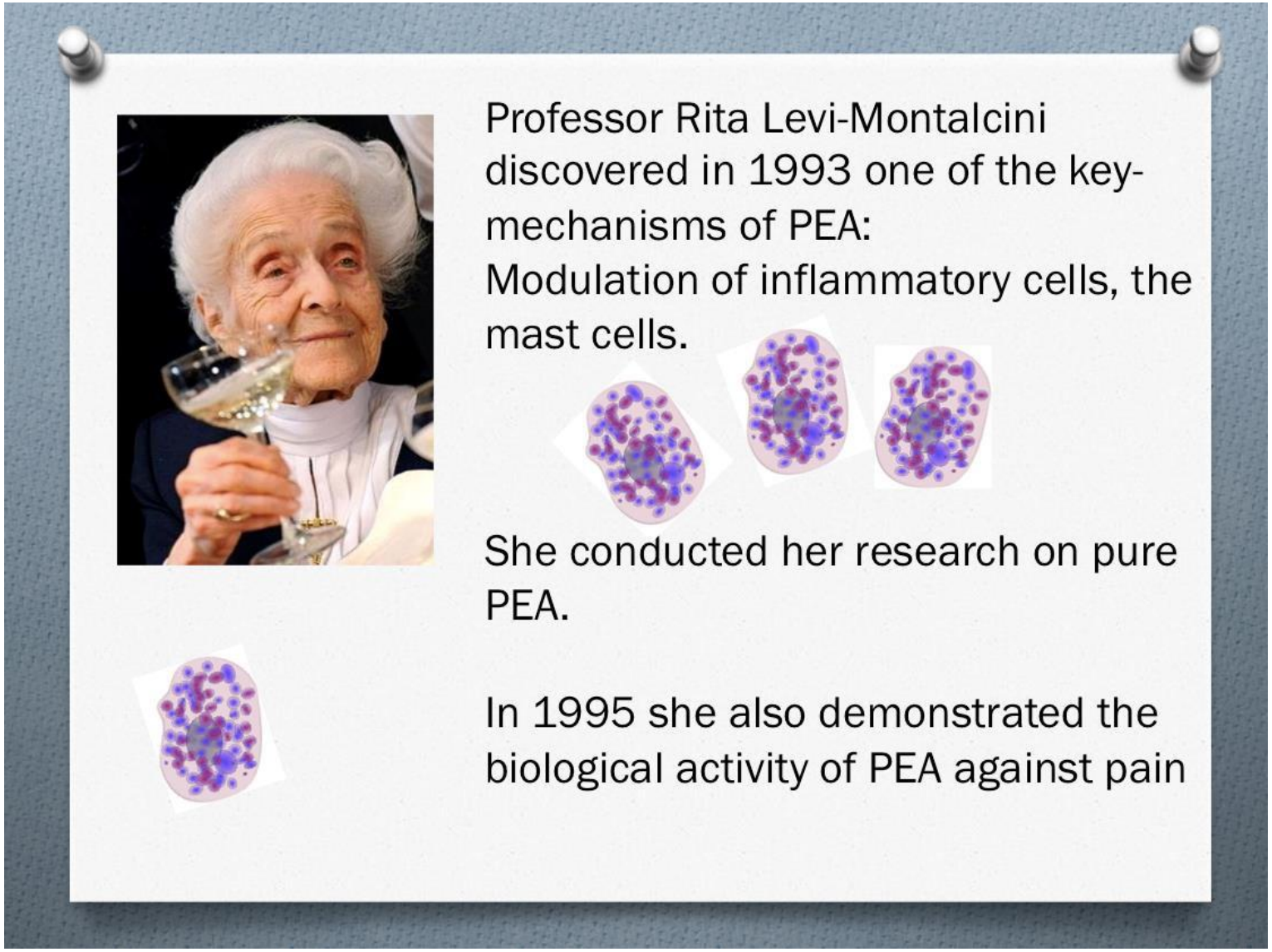
Changes in skin surface hydration over 28 days



Compared with the traditional emollient, the PEA/AEA emollient could simultaneously control both “passive” and “active” skin functions, including regeneration of skin and restoration of lipid lamellae, skin sensation, and immune competence.

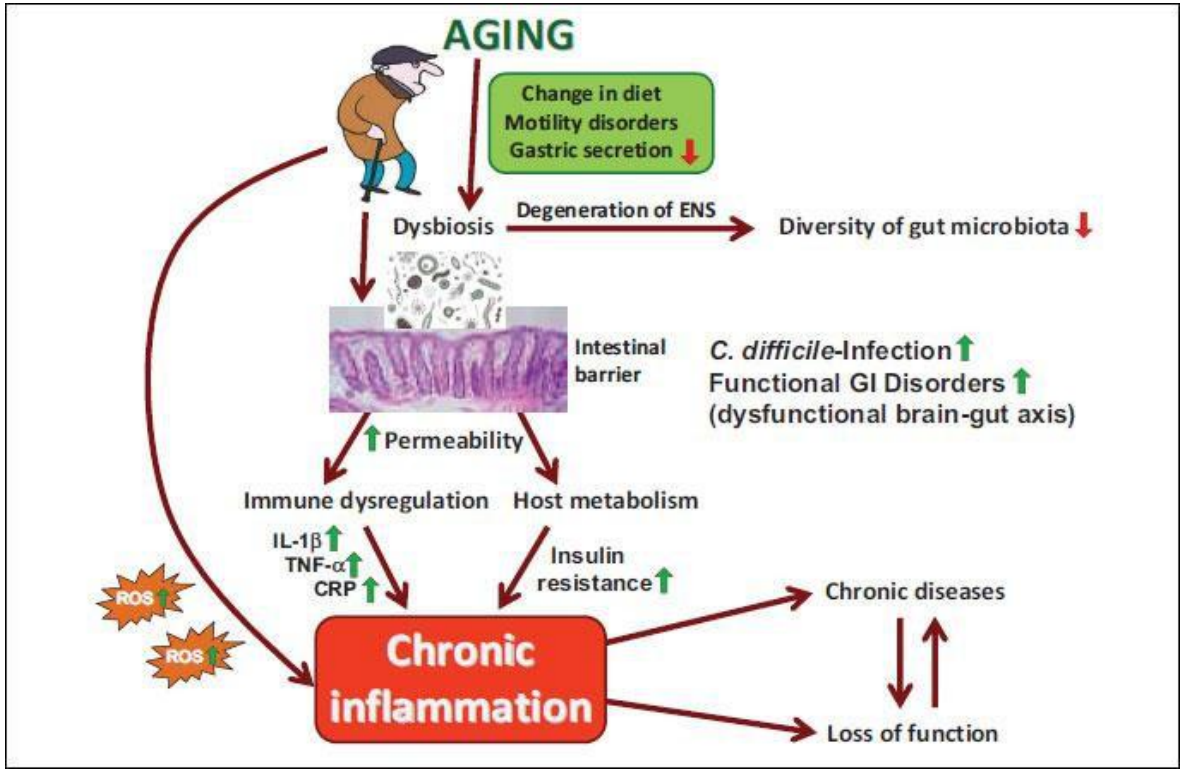
How PEA works

- **The mechanism(s) of action of PEA involve its effects on the nuclear receptor PPARα (Gabrielsson et al., 2016).**
- **It also involves mast cells, cannabinoid receptor type 2 (CB2)-like cannabinoid receptors, ATP-sensitive potassium-channels, transient receptor potential (TRP) channels, and nuclear factor kappa B (NFkB).**
- **It can affect endocannabinoid signaling by acting as a competing substrate for the endocannabinoid homologue anandamide (N-arachidonoylethanolamine).**
- **Gut-brain axis: Role of lipids in the regulation of inflammation, pain and CNS diseases.**



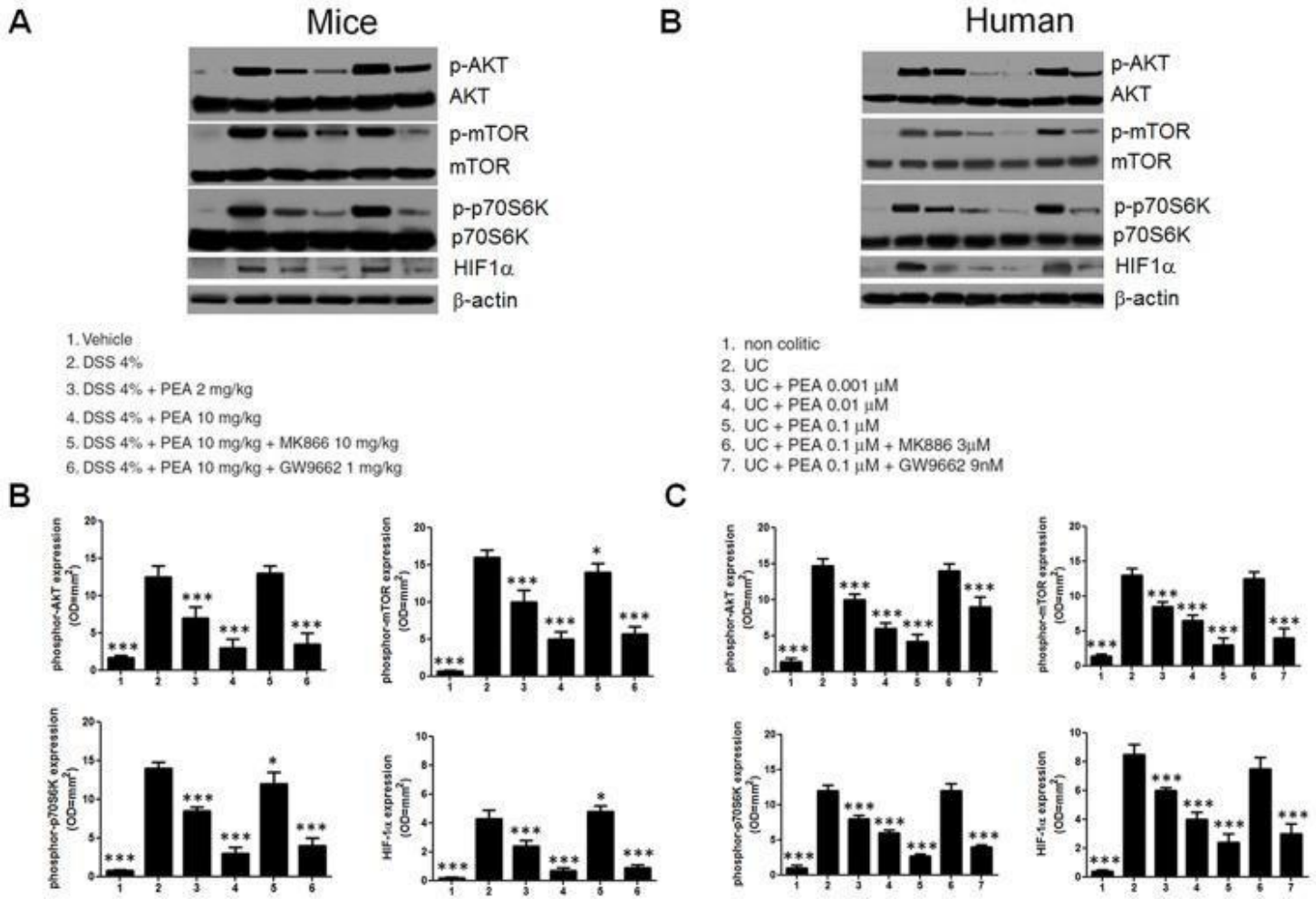
Curr Med Chem. 2017 Feb 16.

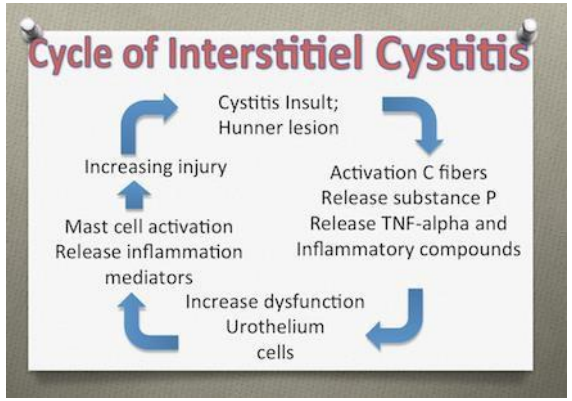
Gut-brain axis: Role of lipids in the regulation of inflammation, pain and CNS diseases.



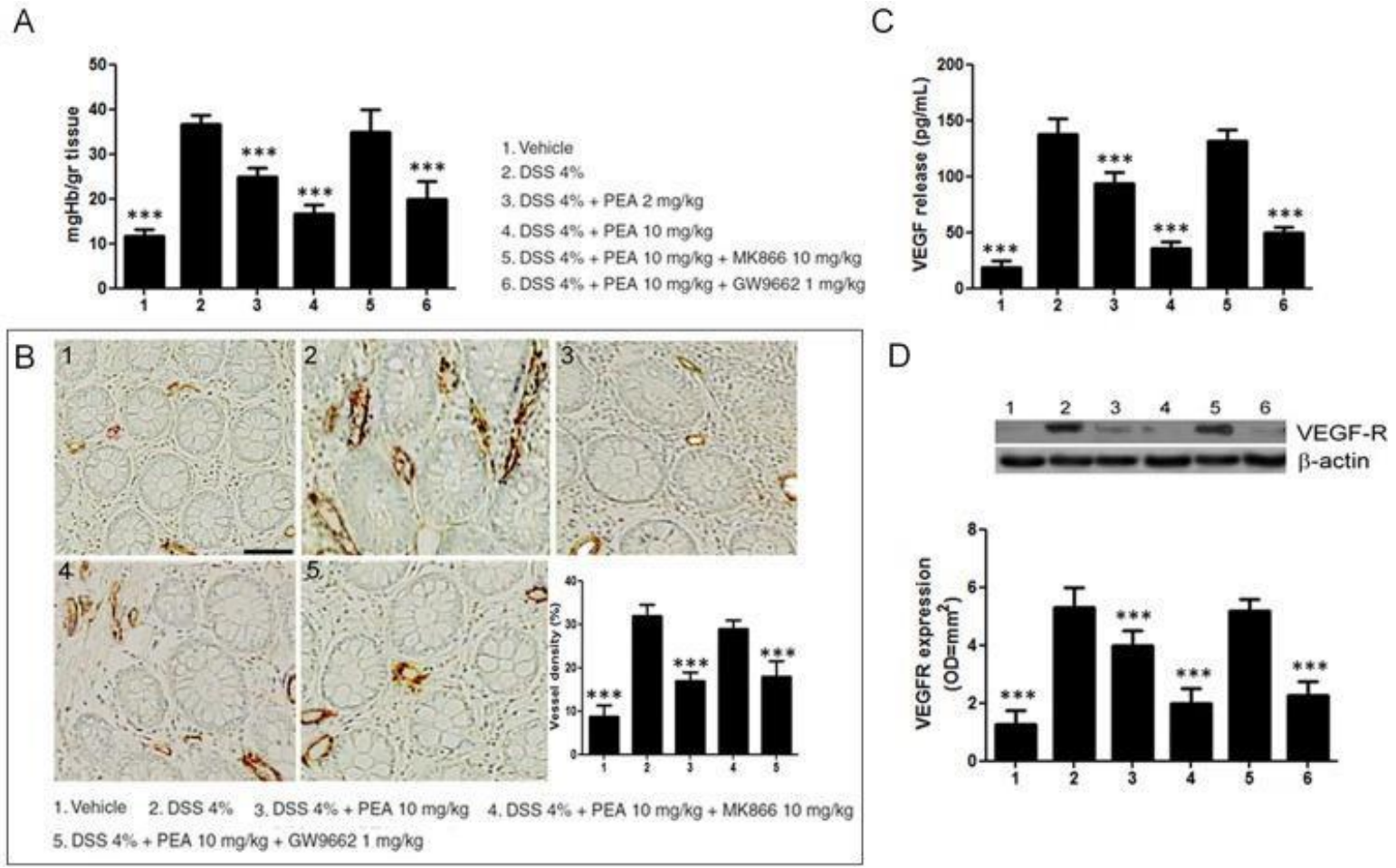
- The human gut is a composite anaerobic environment with a large, diverse and dynamic enteric microbiota, represented by more than 100 trillion microorganisms, including at least 1000 distinct species.
- The discovery that a different microbial composition can influence behavior and cognition, and in turn the nervous system can indirectly influence enteric microbiota composition, has significantly contributed to establish the well-accepted concept of gut-brain axis.
- This hypothesis is supported by several evidence showing mutual mechanisms, which involve the vague nerve, the immune system, the hypothalamic-pituitary-adrenal (HPA) axis modulation and the bacteria-derived metabolites.
- Many studies have focused on delineating a role for this axis in health and disease, ranging from stress-related disorders such as depression, anxiety and irritable bowel syndrome (IBS) to neurodevelopmental disorders, such as autism, and to neurodegenerative diseases, such as Parkinson Disease, Alzheimer Disease etc.
- Based on this background, and considering the relevance of alteration of the symbiotic state between host and microbiota, this review focuses on the role and the involvement of bioactive lipids, such as the N-acylethanolamine (NAE) family whose main members are N-arachidonoylethanolamine (AEA), palmitoylethanolamide (PEA) and oleoilethanolamide (OEA), and short chain fatty acids (SCFAs), such as butyrate, belonging to a large group of bioactive lipids able to modulate peripheral and central pathologic processes.
- It is well established their effective role in inflammation, acute and chronic pain, obesity and central nervous system diseases. It has been shown a possible correlation between these lipids and gut microbiota through different mechanisms. Indeed, systemic administration of specific bacteria can reduce abdominal pain through the involvement of cannabinoid receptor 1 in rat; on the other hand, PEA reduces inflammation markers in a murine model of inflammatory bowel disease (IBD), and butyrate, produced by gut microbiota, is effective in reducing inflammation and pain in irritable bowel syndrome and IBD animal models.
- In this review, we underline the relationship among inflammation, pain, microbiota and the different lipids, focusing on a possible involvement of NAEs and SCFAs in the gut-brain axis and their role in central nervous system diseases.

Effects of palmitoylethanolamide (PEA) on Akt/mTOR/p70S6K axis activation and HIF-1α expression in DSS-induced colitis and in ulcerativecolitis





PLoS One. 2016; 11(5): e0156198.



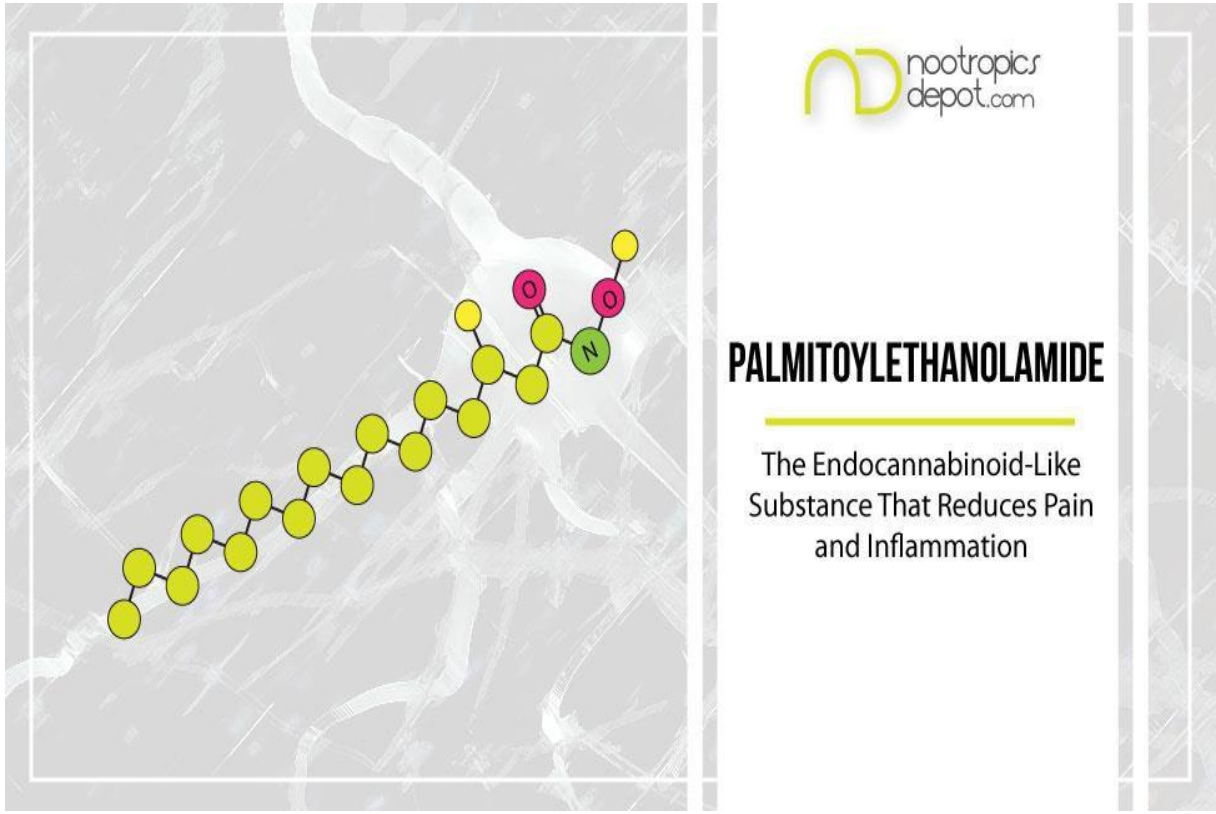
Palmitoylethanolamide (PEA) inhibits colitis-associated angiogenesis in mice. (A) DSS-induced colitis caused a significant increase of Hb-content in colonic mucosa, PEA is able to reduce, in a dose-dependent fashion, the Hb-content in colitis mice; this effect persisted in presence of PPARγ antagonist (GW9662) while it was nullified by PPARα antagonist (MK866). (B) Immunohistochemical images showing the expression of CD31 on untreated mice colonic mucosa (panel 1), DSS-treated mice colonic mucosa (panel 2), DSS-treated mice colonic mucosa in presence of PEA (10 mg/Kg) alone (panel 3), PEA (10 mg/Kg) plus MK866 10 mg/Kg (panel 4), and PEA (10 mg/Kg) plus GW9662 1 mg/Kg (panel 5). Magnification 20X; scale bar: 100μm. The graph summarizes the relative quantification of CD31 expression (%) on mice colonic mucosa in the same experimental groups, showing the reduction of CD31 expression in colitic mice after PEA administration, except for the group also treated with the antagonist of PPARα. (C) VEGF release resulted increase in DSS-treated mice and it was significantly reduced by PEA treatment in a PPARα dependent manner. (D) Western blot analysis and relative densitometric analysis (arbitrary units normalized on the expression of housekeeping protein β-actin) of VEGF-receptor (VEGF-R) expression, showing similar results to VEGF release. Results are expressed as mean ± SD. *p<0.05, **p<0.01 and ***p<0.001 versus DSS-treated mice

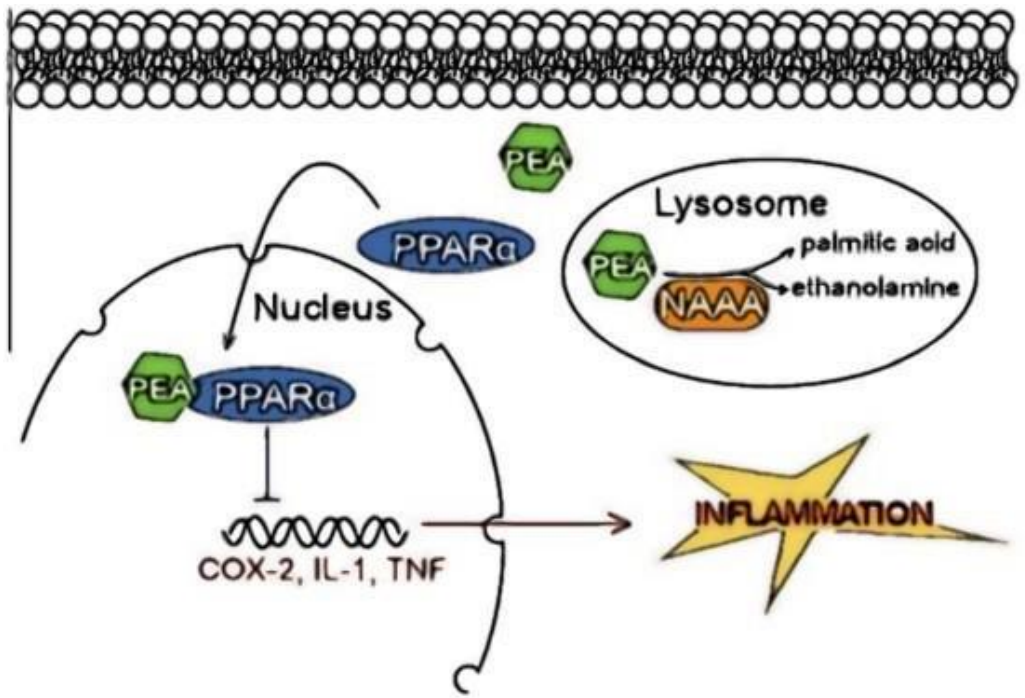
PLoS One. 2016; 11(5): e0156198.

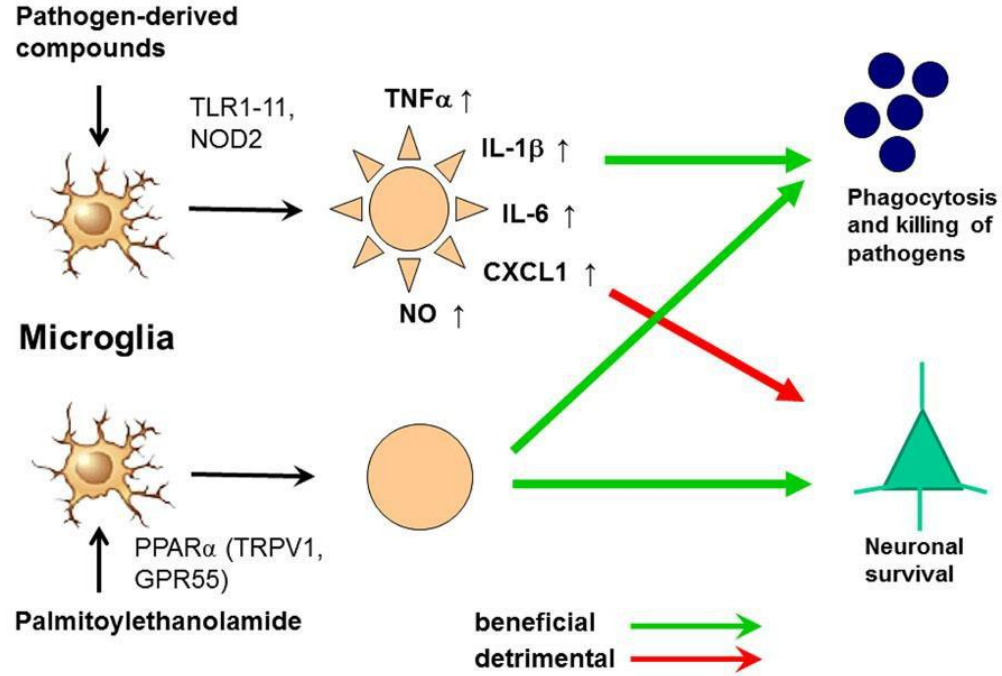
Sci Rep. 2017 Mar 23;7(1):375.

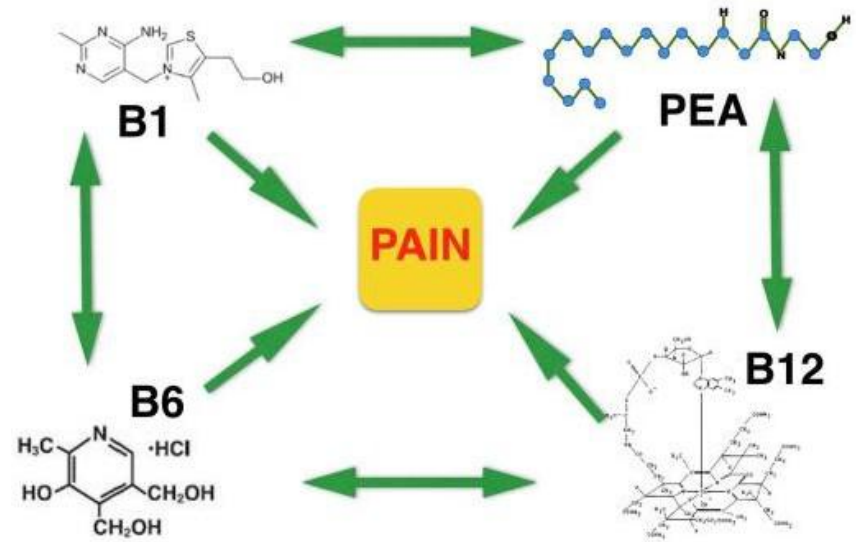
Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor.

- The endogenous fatty acid amide palmitoylethanolamide (PEA) has been shown to exert anti-inflammatory actions mainly through inhibition of the release of pro-inflammatory molecules from mast cells, monocytes and macrophages. Indirect activation of the endocannabinoid (eCB) system is among the several mechanisms of action that have been proposed to underlie the different effects of PEA in vivo.
- In this study, we used cultured rat microglia and human macrophages to evaluate whether PEA affects eCB signaling.
- PEA was found to increase CB2 mRNA and protein expression through peroxisome proliferator-activated receptor-α (PPAR-α) activation.
- This novel gene regulation mechanism was demonstrated through: (i) pharmacological PPAR-α manipulation, (ii) PPAR-α mRNA silencing, (iii) chromatin immunoprecipitation.
    - Moreover, exposure to PEA induced morphological changes associated with a reactive microglial phenotype, including increased phagocytosis and migratory activity.
- Our findings suggest indirect regulation of microglial CB2R expression as a new possible mechanism underlying the effects of PEA. PEA can be explored as a useful tool for preventing/treating the symptoms associated with neuroinflammation in CNS disorders.

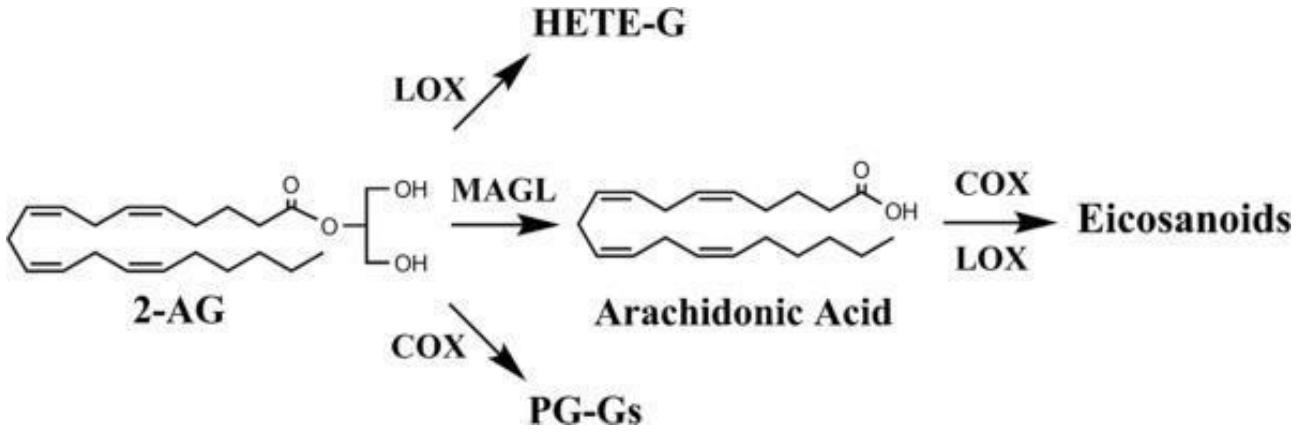






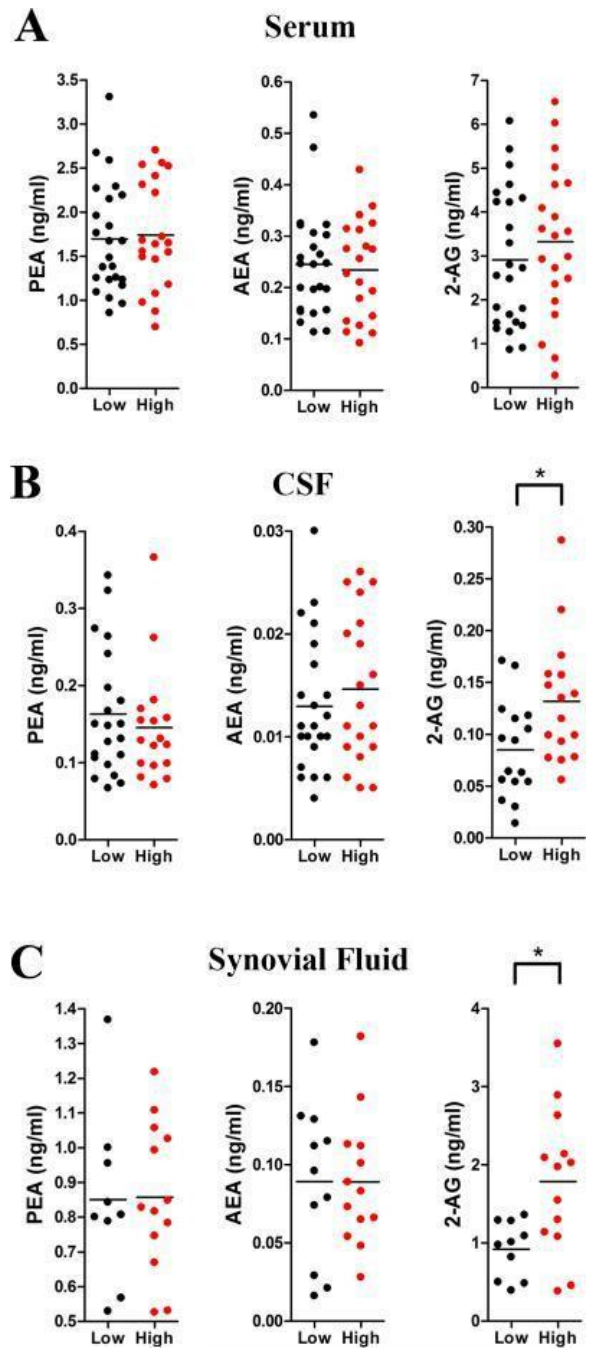


After Kopruszinski et al (2015)
Synergies between B vitamins and PEA against PAIN



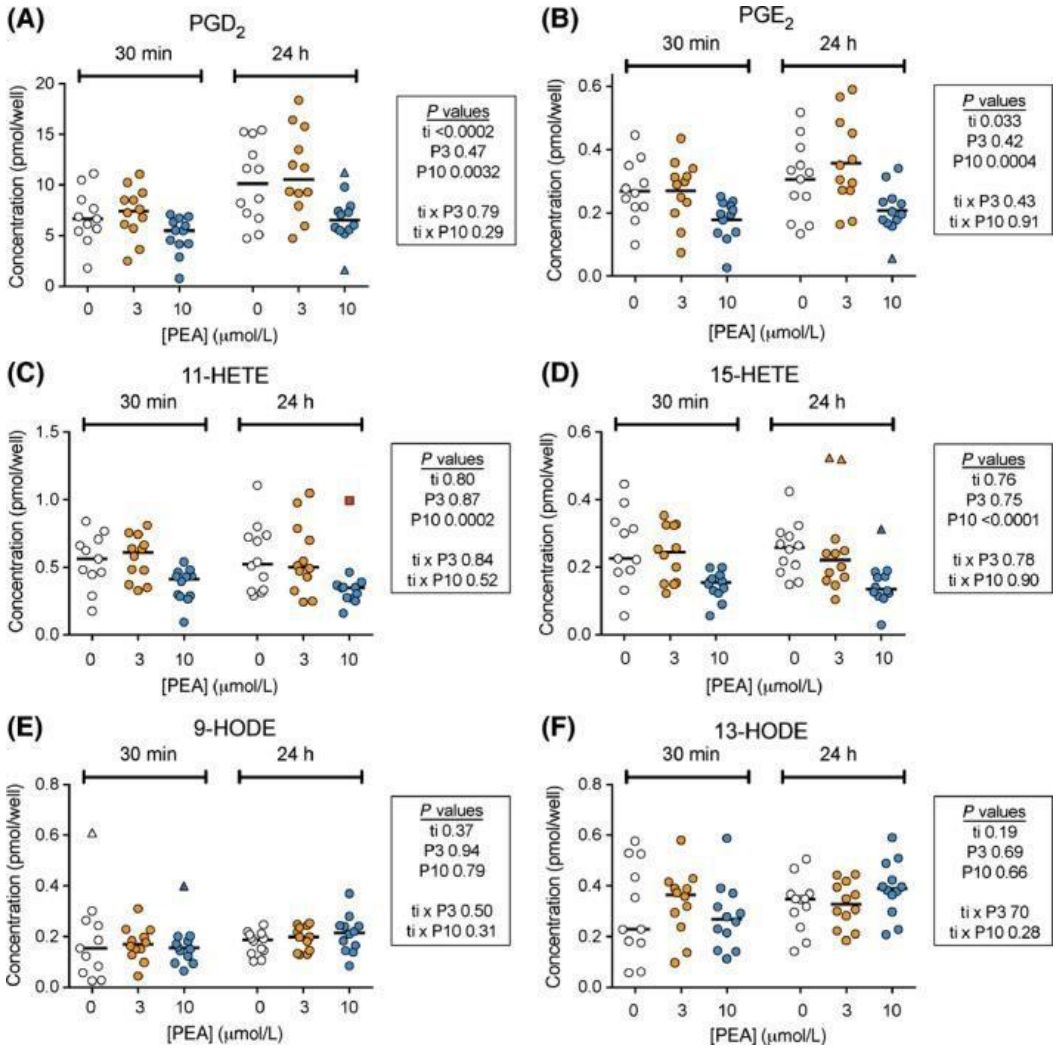
Model of 2-AG metabolism and its possible contribution to post-operative pain. Enzymes that mediate 2-AG metabolism. 2-AG metabolism occurs primarily through hydrolysis by monoacylglycerol lipase (MAGL), yielding arachidonic acid, which is subsequently converted into eicosanoids by COX and LOX enzymes. In addition, 2-AG can be metabolized into prostaglandin glycerol esters (PG-Gs) by COX-2 and hydroperoxyeicosatetraenoic acid glycerol esters (HETE-Gs) by LOX enzymes.

Pain. 2015 Feb;156(2):341-7.



Pharmacol Res Perspect. 2017 Feb 27;5(2):e00300.

The anti-inflammatory compound palmitoylethanolamide inhibits prostaglandin and hydroxyeicosatetraenoic acid production by a macrophage cell line.



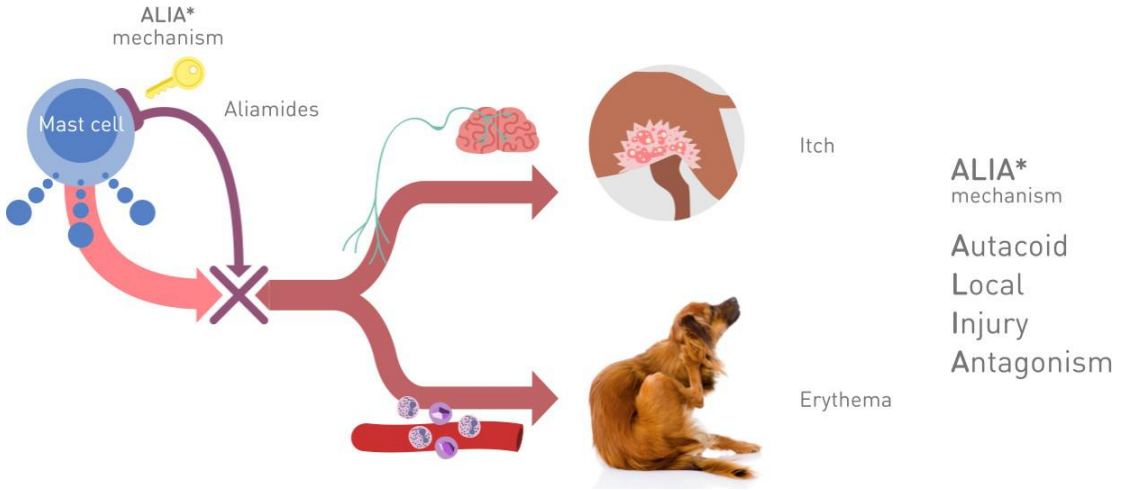
Effect of PEA upon levels of (A) PGD_2; (B) PGE_2; (C) 11-HETE; (D) 15-HETE; (E) 9-HODE and (F) 13-HODE in LPS + IFNγ-treated RAW264.7 cells.

Cells (2.5×10^5 per well) were added to six-well plates with LPS (0.1 μg/mL well) and INFγ (100 U/mL) and cultured at 37° C for 24 h. PEA (3 μmol/L, P3; or 10 μmol/L, P10) or vehicle were added either at the beginning of this culturing period ("24 h") or for 30 min after the LPS + INFγ incubation phase ("30 min").

The *P* values were from linear models for main effects alone (top three rows, *ti* = time component, with 30 min as the reference value) or for a model including interactions (bottom two rows), calculated using *t*-distributions determined by bootstrap with replacement sampling (10,000 iterations) of the data under the null hypothesis. Possible and probable outliers, flagged in Boxplot (Tukey) plots, are shown as triangles and red squares, respectively. The possible outliers were included in the statistical analyses, whereas the probable outlier was excluded. The bars represent median values after exclusion of the probable outlier (n = 11–12). For 11-HETE, the *P* values for the entire data set (i.e. including the probable outlier) were: *ti*, 0.87; P3, 0.86; P10, 0.0020; *ti* × P3, 0.83; *ti* x P10, 0.93.

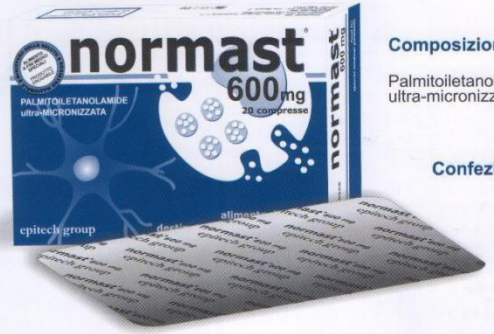
CONSUMPTION OF PEA

- PEA is currently available worldwide in the form of dietary supplements, medical foods, and/or nutraceuticals in different formulations, with and without excipients (Hesselink and Kopsky, 2015).
- PEA is currently marketed for veterinary use (skin conditions, Redonyl™, manufactured by Innovet) and as a nutraceutical in humans (Normast™ and Pelvilen™, manufactured by Epitech; PeaPure™, manufactured by JP Russel Science Ltd.) in some European countries (e.g. Italy, Spain and the Netherlands) (Gabrielsson et al., 2016).
- It also is a constituent of a cream (Physiogel AI™, manufactured by Stiefel) marketed for dry skin (Gabrielsson et al., 2016).
- Ultramicronized PEA is registered as food for special purposes by the Italian Ministry of Health and is not labeled for use in neuropathic pain (Andersen et al., 2015).
- The Food and Drug Administration (FDA) has not previously reviewed the safety of PEA. There are no regulations in the U.S. permitted the use of PEA as a food additive or GRAS substance.



ALIA*
mechanism

Autacoid
Local
Injury
Antagonism



Composizione: *mg per compressa multistrato*

Palmitoiletanolamide ultra-micronizzata 600,00

Confezione: 20 compresse

Brevetto Italia n. 1257697
EU Patent n. 0570714
US Patent n. 5,679,667
EU Patent in progress

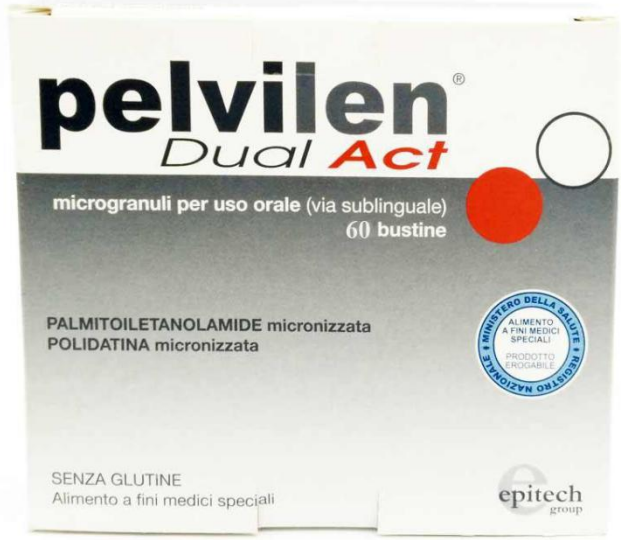
Indicazioni:

normast® 600 trova indicazione:

- negli stati di sofferenza, acuta e cronica, del nervo periferico -anche a livello distrettuale- caratterizzati da elevata attivazione delle componenti spinali;

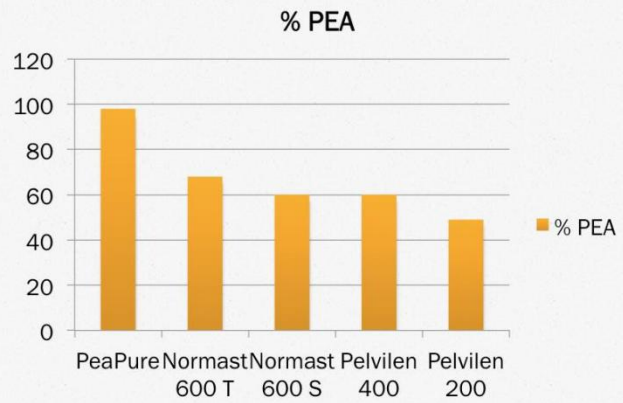
- negli stati di sofferenza del midollo spinale connessi con fenomeni compressivi di diversa origine o con eventi traumatici di natura flesso-estensiva;

egli stati di sofferenza neuropatica dipendente da lesione e/o fiammazione di strutture nervose centrali.



Product	PEA content/serving	Other Stuff
PeaPure 400 mg capsules	100%	None
Normast 600 mg tablets	68%	Chemical excipients
Normast 600 mg sachets	60%	Chemical excipients and sorbitol (385 mg)
Pelvilen 400 mg tablets	60%	Chemical excipients + resveratrol
Pelvilen 200 mg tablets	49%	Chemical excipients + resveratrol
Achilles 100 mg capsules	12%	Heteropterys, Cissus, Zingiber, Siegesbeckia + excipients

ASPECTS	NORMAST	PEAPURE
PEA purity/unit	68%	100%
Units/package	20 tablets	30 capsules
PEA/unit	600 mg	400 mg
Total PEA/package	12 g	12 g
Micronization	+	+
Magnesium-stearate	+	none
Croscaramelose	+	none
Povidone	+	none
Poiisorbate 80	+	none
Silicium col	+	none
GMP-quality	yes	yes



FDA on Medical Food

- In the U.S., medical foods are a special product category regulated by FDA.
  - In Europe, a similar category called “Foods for Special Medical Purposes” (FSMPs) is covered by the Foods for Particular Nutritional Uses directive and regulated by the European Commission (EC).
- In 1988 FDA made steps to encourage the development of the medical foods category by awarding products orphan drug status.
  - These regulatory changes reduce the costs and time associated with bringing medical foods to market, as beforehand medical foods were treated as pharmaceutical drugs.
- Medical foods are not required to undergo premarket review or approval by FDA. Additionally, they are exempted from the labeling requirements for health claims and nutrient content claims under the Nutrition Labeling and Education Act of 1990.
  - Unlike dietary supplements, which are restricted from making disease claims and are intended for healthy individuals, medical foods are intended for specific disease populations.
  - Disease claims must be supported by sound scientific evidence substantiating claims of successful nutritional management of the disease.
  - All ingredients must be approved food additives or classified as GRAS.

FDA on Medical Food

- The U.S. FDA designates medical food as a category of substances intended for the clinical dietary management of a particular condition or disease. Specific criteria necessary to receive this FDA designation include that the product must be:
  - A specifically formulated food for oral or enteral ingestion;
  - For the clinical dietary management of a specific medical disorder, disease or abnormal condition for which there are distinctive nutritional requirements;
  - Made with Generally Recognized As Safe (GRAS) ingredients;
  - In compliance with FDA regulations that pertain to labeling, product claims and manufacturing.
- As a therapeutic category, medical food is distinct from both drugs and supplements.
  - Labels must include the phrase, “to be used under medical supervision,” as medical foods are produced under rigid manufacturing practices and maintain high labeling standards.

Are medical foods the next big trend for packaged foods?

- The opportunities in the medical foods segment are growing; the market is estimated to be worth $15 billion, according to The Wall Street Journal.
- Large food companies, including Nestle and Hormel, are making investments in R&D and product lines to meet medical and nutritional needs.
  - Nestle has put forth a $500 million budget to support medical foods research through 2021.
- As far as challenges, getting the science right and also gaining trust in the health care profession would seem key
  - Ingredient manufacturers should keep up with research in medical science and possibly connect with research universities to get engaged, either to support research or to gain key knowledge.

Specific examples of marketed medical foods and their claimed uses

- Axona (caprylic triglyceride) – Alzheimer's disease[5]
- Banatrol Plus (banana flakes/Bimuno, galacto-oligosaccharide – diarrhea[6]
- Deplin (l-methylfolate) – depression[7]
- Fosteum (genistein aglycone/citrated zinc bisglycinate/cholecalciferol) – osteopenia and osteoporosis[8]
- Limbrel (flavocoxid) – osteoarthritis[9]
- Metanx (L-methylfolate calcium/pyridoxal 5'-phosphate/methylcobalamin) – diabetic neuropathy[10]
- Theramine (l-arginine, 5-htp, histidine, l-glutamine) – myalgia[11]

PEA: Self-Affirmed GRAS (medicinal food ingredient)

- Micronized PEA is intended to be used as a medical food ingredient for the **dietary management of the metabolic mechanisms underlying inflammation-associated chronic pain, angiogenesis, and renal disease as well as physiological mechanisms underlying neuroprotective and retina protective effects of PEA**.
- **PEA is recommended to be used only under medical supervision.**
- **PEA** is proposed for use at a daily dose range of 400 mg/day to 800 mg/day. Typical use is expected to be a starting dose of up to 400 mg BID for 3 - 4 days and a maintenance dose of 300 mg BID for up to 1 year. PEA is not recommended for pregnant and lactating women, children and teenagers. In addition, PEA will not be used in ordinary foods for the general population.