A Decades-Long Journey of Palmitoylethanolamide (PEA) for Chronic Neuropathic Pain Management: A Comprehensive Narrative Review

Supplementary Material

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No.	Title	Justification of the article's importance for the readership	Statement of concrete aims or formulation of questions	Description of the literature search	Referencing	Scientific reasoning	Appropriate presentation of data	Total Score
1	PEA: A Natural Compound for Health Management.	2	1	0	1	0	1	5
2	The Basal Pharmacology of PEA	1	2	1	0	1	0	5
3	Efficacy of PEA for Pain: A Meta-Analysis	1	1	0	1	2	1	6
4	Synaptic Effects of PEA in Neurodegenerative Disorders	2	0	1	1	1	2	7
5	PEA for the treatment of pain: pharmacokinetics, safety and efficacy	1	0	1	2	1	1	5
6	PEA in the Treatment of Chronic Pain: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials	1	2	0	2	1	0	6
7	A Nutritional Approach to Keep Neuroinflammation within Physiological Boundaries-A Systematic Review	2	1	2	0	1	0	6

8	The Effect of PEA on Pain Intensity, Central and Peripheral Sensitization, and Pain Modulation in Healthy Volunteers-A Randomized, Double-Blinded, Placebo-Controlled Crossover Trial	1	2	0	1	0	1	5
9	PEA and Its Formulations on Management of Peripheral Neuropathic Pain	0	2	1	0	0	2	5
10	The pharmacology of PEA and first data on the therapeutic efficacy of some of its new formulations	2	1	1	0	0	0	4
11	Control of pain initiation by endogenous cannabinoids	1	2	1	1	2	1	8
12	PEA: A Natural Body-Own Anti-Inflammatory Agent, Effective and Safe against Influenza and Common Cold	1	1	0	1	2	1	6
13	The cellular immune response of the pea aphid to foreign intrusion and symbiotic challenge	2	0	2	1	2	1	8
14	A randomized controlled trial assessing the safety and efficacy of PEA for treating diabetic-related peripheral neuropathic pain.	1	0	1	2	0	0	4

15	PEA, a Special Food for Medical Purposes, in the Treatment of Chronic Pain: A Pooled Data Meta-analysis	0	1	1	2	1	1	6
16	Clinical applications of PEA in pain management: protocol for a scoping review	2	1	2	2	1	2	10
17	PEA Modulation of Microglia Activation: Characterization of Mechanisms of Action and Implication for Its Neuroprotective Effects	2	1	1	2	1	1	5
18	Glia and mast cells as targets for PEA, an anti-inflammatory and neuroprotective lipid mediator	2	1	0	1	1	0	5
19	Spinal nociceptive sensitization and plasma PEA levels during experimentally induced migraine attacks	0	2	0	1	2	2	7
20	Ultra-micronized PEA: An Efficacious Adjuvant Therapy for Parkinson's Disease	0	2	1	1	2	0	6
21	PEA induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor	1	1	2	1	1	1	7

22	PEA is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR-alpha-mediated mechanism	1	1	2	2	0	2	8
23	Ultramicronized Palmitoylethanolamide (um-PEA): A New Possible Adjuvant Treatment in COVID-19 patients	0	0	1	2	2	1	6
24	PEA is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR-alpha-mediated mechanism	0	1	1	1	1	2	6
25	Effects of PEA on Nociceptive, Musculoskeletal and Neuropathic Pain: Systematic Review and Meta-Analysis of Clinical Evidence	2	1	0	0	2	1	6
26	Effect of PEA on inflammatory and neuropathic pain in rats	1	2	2	1	0	0	6
27	PEA in the treatment of neuropathic pain: a case study	1	2	1	1	1	2	8
28	Effect of Ultra-Micronized Palmitoylethanolamide and Luteolin on Olfaction and Memory in Patients with Long COVID: Results of a Longitudinal Study	2	2	2	0	2	0	8

29	PEA, a nutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome	0	2	1	0	0	0	3
30	Micronized PEA reduces the symptoms of neuropathic pain in diabetic patients	2	0	0	1	2	1	7
31	Non-neuronal cell modulation relieves neuropathic pain: efficacy of the endogenous lipid PEA	2	1	0	0	2	1	6
32	Effect of Ultra-Micronized-Palmitoylethanolamide and Acetyl-l-Carnitine on Experimental Model of Inflammatory Pain	2	0	0	1	2	2	7
33	PEA in homeostatic and traumatic central nervous system injuries	2	1	1	1	2	1	8
34	PEA: problems regarding micronization, ultra-micronization and additives	1	0	1	1	1	1	5
35	Palmitoylethanolamide dampens neuroinflammation and anxiety-like behavior in obese mice	2	1	1	2	1	1	8
36	Heteroarylureas with spirocyclic diamine cores as inhibitors of fatty acid amide hydrolase	1	2	1	1	0	2	7

37	Therapeutic utility of PEA in the treatment of neuropathic pain associated with various pathological conditions: a case series	1	2	1	2	0	2	8
38	Antineuropathic profile of N-palmitoylethanolamine in a rat model of oxaliplatin-induced neurotoxicity	1	1	2	1	0	0	5
39	A novel composite formulation of palmitoylethanolamide and quercetin decreases inflammation and relieves pain in inflammatory and osteoarthritic pain models	1	1	1	1	1	2	7
40	PEA counteracts substance P-induced mast cell activation in vitro by stimulating diacylglycerol lipase activity	0	0	1	1	1	2	5
41	Levels of bioactive endogenous lipids and health-related quality of life in Chronic Idiopathic Axonal Polyneuropathy	2	1	1	1	1	1	7

42	Full inhibition of spinal FAAH leads to TRPV1-mediated analgesic effects in neuropathic rats and possible lipoxygenase-mediated remodeling of anandamide metabolism	0	1	1	0	1	1	4
43	Review of Alzheimer's disease drugs and their relationship with neuron-glia interaction	2	2	2	1	1	2	10
44	Amyotrophic lateral sclerosis treatment with ultramicronized PEA: a case report	2	1	2	0	0	2	7
45	Therapeutic effect of PEA in cognitive decline: A systematic review and preliminary meta-analysis of preclinical and clinical evidence	2	2	2	0	1	1	8
46	An Update of PEA and Luteolin Effects in Preclinical and Clinical Studies of Neuroinflammatory Events	1	2	0	0	0	1	4
47	Effects of Ultramicronized PEA on Mitochondrial Bioenergetics, Cerebral Metabolism, and Glutamatergic Transmission: An Integrated Approach in a Triple Transgenic Mouse Model of Alzheimer's Disease.	1	2	0	1	2	1	7

48	The Association of PEA with Luteolin Decreases Neuroinflammation and Stimulates Autophagy in Parkinson's Disease Model	1	2	1	1	0	1	6
49	Palmitoylethanolamide in CNS health and disease	0	0	2	1	1	1	5
50	Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis	1	1	0	1	0	2	5
51	Plasma endocannabinoid levels in multiple sclerosis	1	2	0	2	1	0	6

Supplementary Table 1: SANRA Score for quality assessment of the selected studies.