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Therapeutic Use of Palmitoylethanolamide (PEA) as an Anti-Inflammatory and Immunomodulator

Maria Clara Inácio de Sá and Marina Gomes Miranda Castor *

Department of Pharmacology, Institute of Biological Sciences, UFMG, Brazil.
* Correspondence: author: Marina Gomes Miranda e Castor - Departament of Pharmacology, ICB-UFMG, Av. Antônio Carlos, 6627 – Belo Horizonte, MG, Brazil, 31.270-100. phone number: +55-31-3409-3048; E-mail: marinacastor@gmail.com.

Abstract: N-palmitoylethanolamine (PEA) is an endocannabinoid-like compound first encountered within lipid fractions of specific foods and has intrigued researchers since the 1950s due to its therapeutic effects. This study aims to explore the therapeutic promise held by PEA as an anti-inflammatory and immunomodulatory agent. Therapeutic impact of PEA reverberates across diverse physiological systems, as the central nervous system, gastrointestinal tract, vascular network, digestive and respiratory system. Additionally, it was effective in pain management, reduction of inflammation and immune responses. These attributes have fostered collaborations targeting conditions such as Alzheimer's disease, multiple sclerosis, cerebral ischemia, neuroinflammation, general inflammation, pain, coagulopathy, steatohepatitis, and acute lung injury. PEA operates both independently and in synergy with other compounds, like paracetamol, luteolin, and oxymetazoline. This efficacy stems from its interactions with pivotal targets including PPARα, PPAR-δ, PPAR-γ, CB1, CB2, GPR55, and TRPV1. Additionally, PEA exerts a direct influence on the inflammatory cascade, orchestrating precise adjustments in immune responses. Numerous animal studies have elucidated the inherent potential of PEA. Nevertheless, the imperative of reinforcing clinical investigation is evident. This review notably underscores the pivotal necessity for methodologically rigorous clinical trials to definitively establish the translational efficacy of PEA in ameliorating diverse inflammatory pathologies within the human milieu.

Keywords: endocannabinoid system; palmitoylethanolamide; inflammation; immune system

1. Introduction

The endocannabinoid system is typically described as being composed of cannabinoid receptors, known as CB1 and CB2, of endogenous ligands referred to as endocannabinoids, and of the enzymes involved in biosynthesis and metabolism processes of these endocannabinoids [1].

Endogenous ligands of cannabinoid receptors are defined as derivatives of polyunsaturated fatty acids, which can be long-chain amides, esters, or ethers capable of binding to and activating these receptors [1]. Anandamide (AEA) was the first endogenous ligand of cannabinoid receptors, initially described in 1992 [2]. In 1995, the 2-arachidonoylglycerol (2-AG) was described. Despite anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the best characterized endocannabinoids, other endogenous compounds capable of binding to cannabinoid receptors have been discovered and suggested to be endocannabinoids: N-dihomo-γ-linolenoyl ethanolamine and N-oleoyl dopamine [1], 2-arachidonoylglycerol ether (noladin ether, 2-AGE) [3], O-arachidonoylethanolamine (virodhamine) [4], and N-arachidonoyldopamine (NADA) and 2-arachidonoylglycerol ether (2-AGE or noladin ether) [5].

Endocannabinoids are produced together with cannabinoid receptor inactive saturated and mono- or di-unsaturated compounds that are defined as endocannabinoid-like compounds. These compounds have been reported to exert their cannabimimetic effect [6]. And, they can also activate cannabinoid receptors, with mechanisms of action that involve synergistic effects, enhancing the effects of classic endocannabinoids, or exhibiting unique properties, such as N-oleoylethanolamine (OEA) [1], Stearoylethanolamide [7,8] and N-palmitoylethanolamine (PEA) [9,10].

Palmitoylethanolamide (PEA) is an endogenous compound initially identified through lipid fractions found in soy, egg yolk, and peanuts [9,10]. It is commonly found in food sources such as soybean sprouts, roasted coffee, black-eyed peas, apples, potatoes [11], and also in human milk [12]. In animals, PEA synthesis occurs through the hydrolysis of its direct phospholipid precursor, N-palmitoyl-phosphatidylethanolamine, by the action of N-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) [13,14].

The pharmacological activities of PEA were first described in the mid-1950s when [10] reported the initial evidence of anti-inflammatory activity and therapeutic properties in anaphylaxis. In 1971, the first report suggested that this exogenous compound could be useful in managing arthritis [15]. Currently, there is evidence supporting its use as an immunomodulator [16], in analgesia [17,18], in managing hypersensitivity [16], and in altering the neurological activities of the central nervous system, such as in Alzheimer's disease [19] multiple sclerosis [20], and sciatic nerve injuries [21]. Furthermore, PEA has significant potential as an anti-inflammatory agent [22]. The mechanism of action of PEA is not fully understood and is based on three hypotheses: local autacoid anti-inflammatory antagonism, direct action mediated by a receptor, or the "entourage" effect [23]. The local autacoid anti-inflammatory antagonism hypothesis suggests that PEA can inhibit mast cell degranulation locally and reduces negative feedback during inflammation [24] . Regarding direct receptor-mediated action, PEA can interact with various receptors, potentially exerting anti-inflammatory and analgesic effects through its interaction with peroxisome proliferator-activated receptors (PPARs) and transient receptor potential vanilloid receptor 1 (TRPV1) [25,26]. It may also interact with G protein-coupled receptor 55 (GPR55), which has anti-anaphylactic effects by acting on mast cells [27]. Interestingly, PEA does not bind to cannabinoid receptors, but it can increase the concentration of anandamide (AEA), enhancing its action [23]. These various therapeutic targets highlight the potencial of PEA as an anti-inflammatory and immunomodulatory tool [22]. Given this context, this research aims to explore the therapeutic utilization of PEA in inflammatory conditions and its immunomodulatory role in various diseases, as well as the correlation of its effects with its pharmacological targets.

2. Materials and Methods

This study was conducted through a specialized search in the PUBMED database using descriptors and Boolean operators. We included systematic reviews, studies involving experimental animal or human models, review articles, and case reports, provided they were freely available in full text in the English language. The search for articles was conducted using the following descriptors: "endocannabinoid system", "endocannabinoid and inflammation", "endocannabinoid and immune system", "endocannabinoid and receptors", "Palmitoylethanolamide", "Palmitoylethanolamide and Inflammation", "Palmitoylethanolamide and immunomodulator", "Palmitoylethanolamide and receptors", without considering the publication year. The literature search was conducted between 2022 (October-November) and 2023 (April-May), resulting in a total of 216 studies. For eligibility criteria, we selected publications that were relevant to the specified descriptors.

3. Endocannabinoid system: a brief review

The endocannabinoid system, despite its relatively recent discovery, plays a fundamental role in the human body's functioning. This system was first identified in the mid-20th century. Its significance is underscored by its widespread distribution throughout the body and its involvement in a variety of physiological processes, including the regulation of pain, appetite, mood, and the immune system [28].

Pioneering studies conducted by researchers like Raphael Mechoulam [29,30] have been instrumental in comprehending this intricate system. Moreover, new components and processes continue to be documented as integral parts of it. Generally, the components of the endocannabinoid system (ECS) include G protein-coupled receptors (CB1 and CB2) [31], their endogenous ligands: classical endocannabinoids (e.g. anandamide or N-arachidonoylethanolamine and 2-

arachidonoylglycerol) and endocannabinoid-like compounds (e.g. PEA, OEA, SEA) [6], and the metabolic enzymes responsible for synthesizing and degrading endocannabinoids [32]. Recently, the orphan G-protein-coupled receptor (GPR55) and two additional classes of receptors have been added to this system, namely the ligand-sensitive ion channels (e.g., Transient Receptor Potential Vanilloid 1 - TRPV1) and nuclear receptors (e.g., Peroxisome proliferator-activated receptors-PPARs) [33,34], as targets for cannabinoid ligands.

Devane et al. in 1992 demonstrated the first cannabinoid receptor in rats, the cannabinoid receptor type 1 (CB1), primarily locating it in the brain [2]. Later on, the cannabinoid receptor type 2 (CB2) was identified through homology cloning, mainly found in the immune system [35]. Actually, CB1 receptors are present in the central nervous system (CNS), which includes the brain and spinal cord. They are highly abundant in regions of the brain associated with memory, cognition, motor function, pain perception, and appetite regulation. Some of the brain regions where CB1 receptors are concentrated include the hippocampus, basal ganglia, and cerebral cortex [32,35]. CB1 receptors are also found in peripheral tissues, such as adipose (fat) tissue, liver, and skeletal muscles. In these peripheral tissues, CB1 receptors are involved in regulating metabolic processes, including lipid metabolism and energy balance. Additionally, CB1 receptors are present in the gastrointestinal tract, where they influence digestive processes and appetite control. The distribution of CB1 receptors in the CNS and peripheral tissues explains their involvement in a wide range of functions, including mood regulation, pain modulation, and appetite regulation [32].

CB2 receptors are primarily found in the peripheral tissues of the immune system. They are highly expressed in immune cells, such as macrophages, T cells, and B cells. CB2 receptors are also present in various peripheral tissues, including the spleen, tonsils, and bone marrow. Their localization in these tissues suggests a role in regulating immune responses and inflammation. CB2 receptors play a crucial role in modulating the immune system's response to injury, infection, and inflammation. Activating CB2 receptors can have anti-inflammatory and immunomodulatory effects [35].

In 1995, Howlett et al., identified the signaling mechanism of the CB1 receptor associated with a G-protein-coupled receptor (GPCR) coupled to Gi/o proteins, which inhibits adenylate cyclase, thereby reducing cellular levels of cAMP [36]. Currently, it is known that signaling pathways in the nervous system can occur in different ways, including retrograde, non-retrograde, or astrocyte-mediated signaling [37].

In the retrograde pathway, the activation of CB1 receptors inhibits neurotransmitter release at synapses through two main mechanisms. In the short term, CB1 receptors are activated for a few seconds, involving direct inhibition, dependent on G-protein (likely through $\beta\gamma$ subunits), of presynaptic Ca2+ influx via voltage-gated Ca2+ channels (VGCCs) [38–40]. For the long term, the predominant mechanism involves the inhibition of adenylate cyclase and negative regulation of the cAMP/PKA pathway through the αi/o subunit [41,42].

In the non-retrograde endocannabinoid-mediated signaling mechanism, the process begins with the production of 2-AG in response to an increase in intracellular Ca2+ concentration and/or activation of Gq/11-coupled receptors [37,43,44]. Subsequently, 2-AG is released and traverses the extracellular space through a mechanism not yet fully elucidated, ultimately reaching the presynaptic terminal where it binds to CB1 receptors. Activated CB1 receptors suppress neurotransmitter release in two ways: first, by inhibiting voltage-gated Ca2+ channels, thereby reducing presynaptic Ca2+ influx; secondly, by inhibiting adenylate cyclase (AC) and the subsequent cAMP/PKA pathway [37,43,44]. This ultimately leads to the degradation of 2-AG by monoacylglycerol lipase (MAGL) [37,43].

In the astrocyte-mediated signaling pathway, postsynaptic neuronal activity leads to the release of endocannabinoids (ECs) that activate astrocytic CB1 receptors coupled to Gq/11 proteins. As a result, PLC activity facilitates astrocytic Ca2+ signaling. Glutamate released from astrocytes activates presynaptic mGluR1s to enhance its release and postsynaptic NMDARs to initiate a slow inward current [37].

The endocannabinoids, in addition to acting on cannabinoid receptors, can exert their effects through ligand-sensitive ion channels like the TRPV1 receptor, nuclear receptors like PPARs, and the orphan G-protein-coupled receptor (GPR55). For this reason, they trigger a series of reactions in multiple signaling pathways involved in both physiological and pathological processes [45].

Among the receptors targeted by endocannabinoids, TRPV1 has been extensively characterized and studied. It is predominantly found in primary afferent nerve fibers [45]. The ion channels of transient receptor potential (TRP) receptors, such as TRPV1, have six transmembrane domains with a pore region located between domains five and six, as well as long intracellular N-terminal and C-terminal domains. Six ankyrin repeat domains are contained in the N-terminal tail, allowing for binding to calmodulin (CaM) and ATP[46]. Furthermore, a TRP domain is present in the C-terminal tail, along with binding sites for calmodulin (CaM) and phosphoinositide 4,5-bisphosphate (PIP2)[46].

TRPV1 plays a crucial role in pain, nociception, and heat perception. It was initially detected in primary afferent nociceptors of the dorsal root ganglia (DRGs), trigeminal ganglia [47], and vagal ganglia. Later, it was also found in regions of the central nervous system, including dopaminergic neurons in the substantia nigra, hippocampus, hypothalamus, cortex, cerebellum, dentate gyrus, and nucleus accumbens. Additionally, it is present in non-neuronal cells such as epidermal keratinocytes, urothelium, hepatocytes, polymorphonuclear granulocytes, pancreatic B cells, endothelial cells, mononuclear cells, smooth muscle cells, mesenteric arteries, pre-adipocytes, and adipose tissue [48] [46].

TRPV1 is characterized by being activated by xenobiotics, including pungent compounds like capsaicin and piperine, high temperatures, and low extracellular pH. Furthermore, it is considerably regulated and/or sensitized under inflammatory conditions and contributes to the initiation or maintenance of intestinal inflammatory processes [49].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that regulate genes crucial in cellular differentiation and various metabolic processes, such as lipid and glucose homeostasis [50]. Following interaction with their specific ligands, a partner receptor, retinoid X receptor (RXR), forms a complex with a variable set of coactivator proteins. The receptors are translocated to the nucleus where they modulate gene expression [50]. The PPAR family comprises three isoforms, α, δ (also known as β), and γ, whose binding recruits additional regulatory proteins involved in transactivation modulation [51].

PPARs play a fundamental role in inflammation, mediating the modulation of the inflammatory response through various mechanisms, such as the inhibition of pro-inflammatory factors (e.g., leukotrienes and interleukins) [52]. Furthermore, it is known that the duration of inflammation tends to be longer in mice deficient in PPARs [53].

These receptors have a wide distribution in tissues. PPARα is found in metabolically active tissues such as the liver and muscle, controlling fatty acid catabolism and participating in inflammatory processes [51]. PPARγ has three subtypes: PPARγ1 is found in brain cells like neurons and glial cells, as well as immune cells derived from the bone marrow; PPARγ2 plays a crucial role in adipocyte differentiation and is restricted to adipose tissue, while PPARγ3 is expressed in macrophages [54]. PPARδ is widely distributed throughout the body and is directly linked to pathological processes such as obesity, diabetes, cancer, neurological disorders, inflammation, dyslipidemia, heart disease, and liver disease [55]. Activation of these receptors can lead to a reduction in the inflammatory response; for example, in asthma, PPARδ activation protects lung tissue by inhibiting leukocyte infiltration and pulmonary fibroblast proliferation [55].

PPARα, in particular, is more directly involved in inflammation, interfering with the action of key inflammatory transcription factors. It acts directly on the pro-inflammatory signaling pathway by affecting NF-κB, activator protein-1 (AP-1), and signal transducers and activators of transcription (STATs). Additionally, this receptor can act through the catabolism of lipid mediators, such as leukotriene B4 (LTB4) [56]. In its active form, PPARα binds to DNA elements, increasing the transcription of various anti-inflammatory proteins, such as IκB-α [57].

G protein-coupled receptors (GPCRs) feature a long protein with three basic regions: an extracellular portion (N-terminal), an intracellular portion (C-terminal), and an intermediate segment containing seven transmembrane domains. When a ligand comes into contact with GPCRs, it induces a conformational change in the transmembrane region, activating the C-terminal, which then activates the G-protein associated with the GPCR. The activated G-protein initiates a series of intracellular reactions, depending on the ligand [58]. GPR55 has been identified in various regions, including the brain, specifically in areas related to memory, learning, and motor functions, as well as in peripheral tissues such as the ileum, testicles, amygdala, breast, omental adipose tissue, and some endothelial cell lineages [59]. Homologs of this receptor have been observed in rats and mice in other brain regions (prefrontal cortex, hippocampus, thalamic nuclei, brainstem, and mesencephalic regions) and in peripheral tissues like the spleen, adrenal glands, and jejunum [46,60].

Below is a summary table of non-cannabinoid binding targets of endocannabinoids.

Table 1. Main non-cannabinoid receptors and endogenous ligands.

MAIN NON-CANNABINOID RECEPTORS AND ENDOGENOUS LIGANDS		
Class	**Target**	**Endogenous component**
GPCR	GPR55	AEA; 2-AG; 2- AGE; Virodhamine
	GPR119	AEA; Oleamide
	GPR118	AEA.
TRP	TRPV1	AEA; 2-AG; 2-AGE
	TRPV8	AEA
Nuclear Receptor	PPARα	AEA; 2- AGE; Virodhamine
	PPARγ	AEA; AG
Voltage-dependent ion channel	Calcium channels	AEA;
	Potassium channels	AEA, 2-AG, Virodhamine.

AEA: anandamide; 2-AG: 2-arachidonoylglycerol; 2-AGE: 2-arachidonoylglycerol ether; GPCR55: G protein-coupled receptor 55; GPCR119: G protein-coupled receptor 119; GPCR118: G protein-coupled receptor 118; TRPV1: Transient Receptor Potential Vanilloid 1; TRPV1: Transient Receptor Potential Vanilloid 8; PPARα: Peroxisome proliferator-activated receptors; PPARγ: Peroxisome proliferator-activated receptors.

4. Palmitoylethanolamide: a promising therapeutic lipid.

In 1965, Bachur   and colleagues identified the presence of Palmitoylethanolamide (PEA) in the brains, livers, and skeletal muscles of rats [61]. Subsequently, a series of studies demonstrated the presence of this lipid fraction in various animal species and in humans, such as canine heart extracts, degenerating tissues, testicles, paw skin, and peritoneal macrophages [62].

PEA is an endocannabinoid-like compound belonging to the N-acylethanolamine (NAE) phospholipid family, isolated from purified lipid fractions of soy, egg yolk, and peanut bran [13]. The structure of PEA comprises a fatty acid (N-Acyl) linked to an amine (ethanolamine), or NAE 16:0, where 16 and 0 refer to the number of carbon atoms and double bonds, respectively, as illustrated in Figure 5. The biosynthesis of PEA begins with the transfer of a fatty acid from membrane-bound phospholipids to phosphatidylethanolamine (PE), catalyzed by a calcium ion and cyclic AMP-regulated N-acyltransferase [63], to form the precursor N-acyl-phosphatidylethanolamine (NAPE). The second step of synthesis involves the cleavage of membrane-bound NAPE to release free PEA, through the action of N-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) [14]. The degradation of PEA into palmitic acid or ethanolamine occurs through the action of two different hydrolytic enzymes, fatty acid amide hydrolase (FAAH), and more specifically, N-acyl-ethanolamine-hydrolyzing acid amidase (NAAH) [64]. Thus, PEA is primarily metabolized to obtain palmitic acid and ethanolamine, through the actions of FAAH and NAAH, respectively. Enzymatic

activities vary depending on the tissue in which they are located [65]. FAAH expression may be higher in the brain and liver, while NAAH is prevalent in the intestine and macrophages [65]. This process of PEA biosynthesis and metabolism can be observed in Figure 6.

4.1. Pharmacokinetic Characteristics

The study of the pharmacokinetic profile of PEA is limited due to its endogenous occurrence and the processes involved in its synthesis and degradation [66,67]. However, despite being a molecule produced by our body, PEA can be administered exogenously. It is known that PEA exhibits a lipophilic character, being practically insoluble in water and sparingly soluble in most aqueous solvents, with a log partition coefficient (log P) greater than 5 [62]. Therefore, the oral absorption of PEA is quite complex, limited by the dissolution rate, showing an inverse relationship with particle size [68].

Most studies concerning the pharmacokinetics of PEA, especially drug absorption, revolve around micronization, which involves reducing the particle size of PEA to increase its surface area for absorption. This is considered an approach to modulate the lipid profile of PEA and enhance its absorption [69]. Torino, et al., 2016 [70] used nanoparticles to extend the anti-inflammatory and analgesic effects of PEA in vivo at the epithelial barrier through a complex of solid and liquid lipids, which increased percutaneous diffusion. In a comparison proposed by Impellizzeri et al. (2014), micronized and ultra-micronized PEA, in an inflammatory pain model in rats, yielded significant results in reducing carrageenan-induced inflammation compared to non-micronized PEA administration [71]. Another interesting study by Petrosino et al. (2018) demonstrated that ultra-micronized PEA was detectable in the bloodstream within 5 minutes of administration, with a peak plasma concentration of 5.4 ± 1.87 pmol/ml, whereas non-ultra-micronized PEA did not produce a significant peak plasma concentration [72]. These studies are intriguing as they show the potential to modulate the lipophilic characteristics of the compound and achieve better therapeutic results. In humans, Petrosino et al. (2016) reported plasma levels of PEA after administering 300 mg of micronized PEA to 10 healthy volunteers at 0, 2, 4, and 6 hours [73]. They observed that PEA plasma concentrations doubled within 2 hours and returned to baseline levels after 4 hours.

The bioavailability of PEA also lacks extensive research, and there is no clear understanding of how the levels of this lipid can vary among individuals. A study conducted by researchers from Umea University (Sweden) estimated the plasma concentration, volume of distribution, and half-life of PEA after oral treatment of male Wistar rats with 100 mg/kg of PEA in a corn oil suspension. The authors demonstrated that bioavailability of PEA was low, around 25%, but the volume of distribution exceeded the plasma volume, indicating that most of the PEA would be outside the blood after oral administration [65,74].

PEA distribution was described in the study by Zhukov et al. (1999) after the intraperitoneal administration of radiolabeled PEA in rats [75]. The lipid compound exhibited distribution, especially in some peripheral organs such as adrenal glands, diaphragm, spleen, kidney, testis, lung, liver, and heart, with lower concentrations detected in the brain and plasma. In a more recent study, the administration of PEA emulsified with sterile corn oil injected into male mice showed elevated basal levels in the retina compared to blood serum, heart, and brain. These data highlight the ability of PEA to cross the blood-brain barrier, suggesting its involvement in brain function, particularly in regulating the response to stress through the hypothalamus-pituitary-adrenal system [76]. Additionally, regarding distribution of PEA in the body, [77] analyzed seven human placentas, amniotic and amniochorionic membranes, placental disc, umbilical cord, umbilical serum, and vernix caseosa collected after cesarean delivery to determine endogenous PEA concentrations in tissues. The authors found the presence of the lipid compound in all analyzed tissues, with a higher prevalence of PEA in the amniotic membrane and lower concentrations in the umbilical cord and vernix.

PEA metabolism involves the formation of palmitic acid and ethanolamine through the action of the enzymes FAAH and NAAH, and this inactivation process occurs through lipid hydrolysis [78]. FAAH is an intracellular membrane-bound serine hydrolase, predominantly identified in mammalian tissues, with higher abundance in the brain and liver [79]. NAAH is a cysteine hydrolase

present in cellular lysosomes or the Golgi apparatus, activated under acidic pH conditions, showing greater selectivity for PEA [1]. The enzyme is expressed in various blood cell lineages, macrophages, and various rodent tissues, with higher prevalence in humans in leukocytes, liver, spleen, kidney, and pancreas [1].

The excretion of PEA remains unclear, and the mechanisms by which the orally or topically administered compound is hydrolyzed into palmitic acid are unknown [69]. To date, the only known information is related to its protective role in the kidney in hypertensive injury in rats, involving the reduction of the expression of the enzyme epoxygenase CYP2C23 and soluble epoxide hydrolase. This reduction is accompanied by a significant decrease in renal oxidative and nitrosative stress, along with a decrease in renal expression of NAD(P)H oxidase and inducible nitric oxide synthase, and an increase in the expression of Cu/Zn superoxide dismutase, as demonstrated by Mattace, et al., 2013 [80].

4.2. Possible Pharmacological Targets and Mechanisms of Action

Action of PEA involves three possible mechanisms. The first suggests that the lipid compound can negatively regulate mast cell degranulation through an effect called "Autacoid Local Inflammatory Antagonism" (ALIA). The second proposition states that this component can act through the "entourage effect," enhancing the pharmacological activities of AEA. Finally, it can stimulate receptors similar to cannabinoids, such as PPAR-α and GPR55 [81]. Understanding the multiplicity of targets is the key to PEA, as its therapeutic effects can be attributed to a single mechanism or several primary targets [69].

The first hypothesis about action of PEA emerged from studies by Aloe et al. (1993) [24]. They conducted an animal model study with Sprague-Dawley rats treated with long-chain and short-chain N-acylethanolamines during inflammation induced by a substance called "P." The authors observed a local antagonism in inflammation called ALIA, suggesting a local autocrine/paracrine contribution to the control of negative feedback from mast cell responses to various activation signals. Subsequently, Mazzari et al. (1996) demonstrated the correlation of anti-inflammatory activity with the negative regulation of mast cells in an experimental model of male rats and female mice induced by paw edema and carrageenan-induced hyperalgesia treated with palmitoylethanolamide [82]. Scarampella et al. (2001) obtained similar results when observing an increase in the granular density of cutaneous mast cells in a population of cats, including males and females of different ages. In total, 15 animals with diagnoses of eosinophilic granuloma and eosinophilic plaque were treated with 120 mg of palmitoylethanolamide, and clinical improvement in the lesions was observed, suggesting that PEA could be an alternative to corticosteroid therapy for these skin conditions [83]. It is interesting to note that these mechanisms demonstrate the ability of PEA to act in the Down Regulation process, an important pathway in controlling mast cell hyperactivity in inflammatory processes and inflammatory and neuropathic hyperalgesia [84].

The entourage effect proposes that PEA act enhancing the antinociceptive and anti-inflammatory activities of other endogenous compounds by increasing their affinity for receptors or by inhibiting their metabolic degradation [28,85]. One of these endogenous compounds is AEA, whose activity can be potentiated by PEA to increase pharmacological effects, as demonstrated by Ho, Barrett & Randall (2008) in an experimental model with male Wistar rats studying the third-order branches of the superior mesenteric artery [86]. The removed vessels were pre-contracted with methoxamine and treated with anandamide, PEA, or OEA. To assess the activation of TRPV1, the authors used capsaicin. They observed the ability of PEA to potentiate vasorelaxation, indicating that pretreatment with PEA enhanced the vasorelaxant effects of AEA through TRPV1 receptor activity.

Endogenous PEA can also be synergistically stimulated through the administration of exogenous compounds when given orally, as proposed by Del Re et al. (2022) [87]. In an experimental mouse model, after administering Adelmirol, a semi-synthetic analog of PEA, the authors observed an increase in N-acylethanolamide concentrations in the duodenum and colon of the animals, increasing endogenous PEA levels in a dose/time-dependent manner. This also regulated the enzymatic machinery responsible for the metabolism and catabolism of this lipid compound.

Lastly, PEA can act on pharmacological receptors such as TRPV1, PPARs, and GPR55, which are involved in the mechanism of action of other cannabinoids like AEA, 2-AG, and the ether 2-arachidonoylglycerol [1].

4.2.1. PEA interaction with transient receptor potential vanilloid type 1 (TRPV1)

Action of PEA through the TRPV1 receptor is well-discussed, and the widespread distribution of the receptor in tissues may be responsible for its therapeutic effects. De Petrocellis et al. (2002) conducted an *in vitro* study that examined PEA and AEA activities in intracellular Ca^{2+} binding assays, VR1 receptor binding assays, and AEA hydrolase activity assays [88]. These authors synthesized these compounds from arachidonic acid or palmitic acid and ethanolamine. They observed an increase in AEA-mediated VR1 action in [Ca2+]i, suggesting an intensification of AEA actions mediated by TRPV1. Ambrosino et al. (2013) reported similar results from an *in vitro* study using F11 and CHO cells in pain inducers like capsaicin (CAP) or bradykinin (BK). They observed a molecular mechanism for action of PEA on TRPV1. They proposed that the activation of TRPV1 channels by ethanolamide triggers membrane depolarization, leading to a substantial increase in [Ca2+]i [89].

Petrosino et al. (2016) also identified the action of PEA on TRPV1 channels *in vitro*, finding that its mechanism increases 2-AG activation and desensitizes intracellular Ca^{2+} elevation mediated by TRPV1 [73]. They also observed an increase in 2-AG in human keratinocytes and dogs. HO et al. (2008) correlated the effect of PEA with its action on TRPV1. In this study, PEA administration in Wistar rats significantly increased anandamide levels, enhancing vessel relaxation [86]. In an experimental model of intestinal inflammation induced by intracolonic administration of mustard oil in mice treated with PEA, Capasso et al. (2014) observed that PEA reduced colon peristalsis. The authors proposed that this effect could be due to TRPV1 and CB1 receptor activation, as the compound increased anandamide levels [90]. Another link between PEA and intestinal inflammation in rats was proposed by Borrelli et al. (2015), where exogenous lipid compound reduced neutrophil infiltration, decreased intestinal permeability, and stimulated colonic cell regeneration, also increasing colonic TRPV1 and CB1 receptor expression. These studies suggest that the effect of PEA may be related to TRPV1 receptor activation [68].

4.2.2. PEA interaction with peroxisome proliferator-activated receptor (PPARs)

PEA has been extensively studied for its interaction with PPARα (peroxisome proliferator-activated receptor alpha), a nuclear receptor that plays a crucial role in regulating inflammation and various metabolic processes. This interaction is a key mechanism underlying the anti-inflammatory effects of PEA and its potential therapeutic benefits in several medical conditions. In a mouse model of carrageenan-induced paw edema, intracerebroventricular administration of PEA led to the control of peripheral inflammation by activating PPARα. This resulted in a significant reduction in pro-inflammatory enzymes like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase [91,92].

PEA interaction with PPARα is not limited to its anti-inflammatory activities. Studies have demonstrated its involvement in various physiological processes. For instance, PEA has been shown to restore the plasticity of brown and white adipocytes in mice fed a high-fat diet, with PPARα activation playing a crucial role in this process. Additionally, PEA improved mitochondrial bioenergetics and induced metabolic machinery through AMP-activated protein kinase (AMPK) phosphorylation [93].

The therapeutic potential of PEA extends to conditions such as retinopathy, where it significantly reduces inflammation, inhibits neovascularization in the retinas, and suppresses pro-fibrotic changes and Müller gliosis. The positive effects of PEA in these contexts have been associated with an increase in PPARα expression [94].

Furthermore, PEA has been investigated for its potential use in pain management. Studies have suggested that PEA, when combined with other drugs like morphine or gabapentin, may produce synergistic effects in relieving inflammatory pain, mediated through PPARα receptors [91].

Combining PEA with tramadol also reduced sedation while enhancing its analgesic effect, further highlighting its potential synergistic actions involving TRPV1 and PPAR-α receptors [95].

Anti-tumor activity of PEA has been linked to PPARα and GPR55 receptors. In studies conducted on mice, PEA inhibited tumor cell proliferation, induced cell cycle arrest at the G2/M phase, reduced DNA fragmentation, and suppressed cell migration. These effects were mediated by PPARα activation and inhibition of the AKT/mTOR cell cycle pathway [96].

Thru activation PPARα, PEA has also demonstrated a neuroprotective effect in animal models of neurodegenerative diseases such as Parkinson's and Alzheimer's disease. Its actions involve anti-inflammatory mechanisms, modulation of pro and anti-apoptotic markers, and protection against neuronal damage [97,98]. In addition to its role in inflammation and neuroprotection, PEA has shown promise in addressing behavioral symptoms associated with autism spectrum disorder (ASD). In mouse models of ASD, PEA treatment was found to reverse abnormal behavioral phenotypes by acting on PPARα and reducing overall inflammation and pro-inflammatory cytokine expression [99].

Indirect activation of cannabinoid receptors, mainly (CB2), by PEA, has also been linked to its PPARα-mediated effects. This interaction is relevant in the context of neuroinflammatory disorders, where PEA may modulate microglial activity and migration [100].

Overall, interaction of PEA with PPARα is a multifaceted mechanism that underlies its diverse therapeutic effects, ranging from anti-inflammatory and analgesic properties to neuroprotection and metabolic regulation. These findings highlight the potential of PEA as a valuable compound in various medical applications.

4.2.3. Interaction of PEA with G protein-coupled receptors (GPR55)

PEA is a potent and selective agonist at the GPR55 receptor [60]. The authors demonstrated the expression of the GPR55 receptor in mouse tissues, where receptor mRNA was found in the adrenal glands, gastrointestinal tract, as well as in the central nervous system (CNS) of the animals modulating diverse physiological functions mainly involved with inflammatory and immune response.

Inflammation induced by atherosclerotic plaques was the subject of study by Rinne et al. (2018) in adult male and female mice deficient in GPR55 treated with palmitoylethanolamide at 3 mg/kg via intraperitoneal injection for 4 weeks [101]. The authors observed that PEA, upon activating GPR55, increased the expression of the MerTK phagocytosis receptor (proto-oncogene tyrosine-protein kinase MER), as well as enhancing macrophage efferocytosis. However, they emphasize that this anti-inflammatory process is multifactorial and may also be mediated by PPAR-α [101].

Marichal-Cancino et al. [102] demonstrated in Wistar rats that intravenous administration of PEA inhibits vasopressor responses to sympathetic stimulation and exogenous norepinephrine and induces hypotension, which may be correlated with its effects on GPR55, in addition to its action on CB1 and TRPV1 receptors.

In an in vitro organ culture model with porcine eyes, Kumar et al. [103] demonstrated that PEA can increase the aqueous humor outflow through the trabecular meshwork [79] pathway, and these effects are mediated by GPR55 and PPARα receptors through the activation of p42/44 MAPK.

5. Therapeutic opportunities of palmitoylethanolamide

PEA demonstrates significant therapeutic potential for inflammation, primarily due to its ability to modulate the immune system. Numerous articles discuss research approaches and confirm these findings.

5.1. Therapeutic Potential of PEA in Central Nervous System Disorders

The spinal cord injury has been used to assess the therapeutic performance of PEA to treat injury of the central nervous system, as demonstrated by Genovese et al. (2008) [104]. The researchers showed that intraperitoneal administration of PEA in mice exhibited anti-inflammatory and immunomodulatory activity, reducing the severity of spinal cord trauma and significantly improving

functional deficits. Furthermore, PEA attenuated neutrophil infiltration, decreased levels of TNF-α and IL-1, reduced iNOS expression, nitrotyrosine, and also prevented IκBα degradation and reduced Ser536 phosphorylation of the p65 subunit, NF-kB levels in the p65 subunit, and cell death [104].

Another interesting study involving spinal cord injury was conducted by Crupi et al. (2016) with the intraperitoneal administration of the co-ultraPEALut compound in mice. Co-ultraPEALut presented regenerative capacity and an immunomodulatory profile promoted functional recovery, stimulated dendritic tree remodeling in the injured area, and restored the regulation of neurotrophic factors, such as, brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) [105] . Co-ultraPEALut can also be used in cerebral ischemia, as proposed by Caltagirone   et al. (2016) [106]. Using an experimental rat model Co-ultraPEALut reduced cell death in a hippocampal area, decreasing damage-induced GFAP expression, increasing levels of neurotrophic factors such as BDNF and GDNF, and attenuating chymase and tryptase expression [106]. In Caltagirone et al. (2016) the authors continued the study by testing Co-ultraPEALut in humans aged 31 to 100 years after a stroke. The 700 mg of ultramicronized PEA with 70 mg of luteolin (Glialia®), administered sublingually for 30 days improved cognitive function, patient independence and mobility and overall muscle spasticity. The authors reported no adverse reactions or deviations in hematological and chemical analyses of the patients. However, a controlled trial is needed to better assess the clinical performance of the compound [106].

Paterniti et al. (2013) also addressed spinal cord injury in mice. PEA administration showed anti-inflammatory and neuroprotective properties. This action may involve the activation of PPAR-δ, PPAR-α, and PPAR-γ, which would also be correlated with the inhibitory potential of PEA on neutrophil infiltration. PEA restored physiological levels of TNF-α and IL-1β, but genetic absence of PPAR-α and the use of a PPAR-δ or PPAR-γ antagonist reversed the reduction induced by PEA. The lipid compound also showed the potential to attenuate iNOS expression and restore PPAR-γ and PPAR-δ levels in the spinal cord Paterniti et al. (2013) [25].

A sciatic nerve injury model was proposed by Gugliandolo et al. (2018) with the oral administration of palmitoylethanolamide with oxazoline (PEA-OXA) to mice [21]. PEA-OXA displayed anti-inflammatory and neuroprotective activity, reduced edema, mast cells infiltration, c-Fos protein expression, and the presence of NAAA. As well as restricting the pain threshold and increasing β-tubulin class III (β-III-tubulin) expression. A reduction in IκB-α degradation and Nf-κb translocation was also observed, along with a reduction in TNF-α, IL-1β, glial fibrillary acidic protein (GFAP), and ionized calcium-binding adapter molecule 1 (Iba-1) and the apoptotic process, promoting better functional recovery of the sciatic nerve   [21]. Di Cesare Mannelli et al. (2013) also addressed the experimental sciatic nerve injury model in mice, with PEA administered subcutaneously. The main finding of the study involved the anti-inflammatory and neuroprotective activity of the fatty acid derivative. It was observed that PEA prevented cellular infiltration and alterations in pain threshold mediated through the PPAR-α receptor. Additionally, PEA significantly prevented the increase in COX2 [107].

PEA-OXA performance and mechanism was also tested in a rat model of cerebral ischemia, in diabetic rats, treated intravenously. This study conducted by Fusco   et al. (2019) demonstrated a reduction in tissue damage, mast cell infiltration and degranulation, apoptosis, NF-κB translocation to the nucleus, NF-κB and TGF-β expression. Additionally, the authors also noted the ability of PEA-OXA to reduce TNF-α and IL-1β and increase the expression of neurotrophic factors such as BDNF and GDNF. These effects were correlated with the activation of silent information regulator 1 (SIRT-1) [108].

5.1.1. Neuroinflammation

Neuroinflammation is characterized by an inflammatory response that affects the brain or spinal cord, mediated by the production of cytokines, chemokines, reactive oxygen species, and secondary messengers produced by glial cells such as astrocytes and monocytes, as well as by endothelial cells and peripherally-derived immune cells [109]. This process leads to changes in the central nervous

system (CNS), such as decreased neurogenesis, increased apoptosis, activation of astrocytes and microglia, disruption of the blood-brain barrier (BBB), increased synthesis of Aβ, tau phosphorylation, among others, and plays a significant role in the development of conditions like Alzheimer's disease (AD) and multiple sclerosis [110,111].

Hohmann et al. (2019) and Scuderi et al. (2011) in an *in vitro* model of co-cultured astrocytes and microglia showed the performance of PEA to control the neuroinflammation. PEA displayed a neuroprotective role attenuating Aβ-induced astrocyte activation, reducing the expression and release of all detected pro-inflammatory molecules, such as nitric oxide, IL-1β, TNF-α, and prostaglandin E_2 (PGE_2). It also showed an inhibitory potential on MAPK phosphorylation and nuclear transcription factors NF-κB and AP-1, and all of these effects were prevented when a PPAR-α receptor antagonist was used [112,113] . D'Aloia et al. (2021) also proposed an *in vitro* neuroinflammation model using microglial cells (N9) induced by lipopolysaccharide (LPS). In this model was observed that the fatty acid derivative neutralized the polarization of M1 microglia, antagonized the stimulation of mRNA production for pro-inflammatory cytokines, increased IL-10, reduced TNF-α in the culture medium, and the cellular content of pro-IL-1β. Another interesting factor observed was the ability of PEA to inhibit the ATP-induced intracellular Ca^{2+} increase in N9 cells and primary microglial cells D'Aloia. [114].

Furthermore, in an experimental rat model, intraperitoneal administration of PEA had a neuroprotective and anti-inflammatory effect [91]. The fatty acid derivative reduced TNF-α expression, p65 transcription factor, inducible nitric oxide synthase [91] mRNA, and prevented the regulation of prostaglandin E synthase-1 (mPGES-1) and PGE_2. In addition, the authors observed that PEA prevented the accumulation of malondialdehyde, a marker of lipid peroxidation.

Another interesting study addressed the anti-inflammatory of effects PEA, added to the diet of obese mice, in anxiety-related neuroinflammation [115]. The authors observed that PEA neutralized systemic inflammation by reducing serum TNF-α and IL-1β levels, as well as improving anxiety behavior by modulating dopamine renewal and gamma-aminobutyric acid (GABA) levels in the amygdala. The authors also reported the ability of PEA to neutralize microgliosis and astrogliosis and to restore Blood Brain Barrier (BBB) integrity, confirming the role of PPAR-α in the therapeutic activity of PEA.

In a mouse model of intracerebral hemorrhage (ICH), PEA administered intraperitoneally exhibited an anti-inflammatory role, as discussed by Zhou et al. (2022) zhou [116]. PEA improved neurological and motor function, attenuating NF-κB, IL-1β, and TNF-α, a mechanism correlated with the PPAR-α receptor. A notable factor in the study was the ability of PEA to increase the percentage of the anti-inflammatory microglia phenotype to exert a neuroprotective effect.

One way to enhance the effects of PEA is by adding luteolin in an ultramicronized formulation (co-ultraPEALut), as evidenced by Paterniti et al. (2013) [117]. When injected intraperitoneally into mice, this compound exhibited anti-inflammatory activity and the ability to reduce apoptosis, decrease cyclooxygenase-2 (COX-2) and nitric oxide (NO) expression, effects that were concentration-dependent. It also resulted in a significant increase in the expression of PPARα, PPARβ/δ, and PPARγ.

5.1.2. Alzheimer's Disease

Alzheimer's Disease (AD) is recognized by the World Health Organization as a global public health priority, primarily because there is still no disease-modifying drug available [118]. PEA can also be useful in Alzheimer's disease due to its potential to improve learning and memory deficits, given its anti-inflammatory and neuroprotective properties, as proposed by Scuderi et al. (2018) [119]. The authors addressed the pathology in an experimental mouse model by subcutaneously administering micronized PEA, demonstrating its ability to reduce the formation of Beta-amyloid (Aβ) plaques and reduce tau phosphorylation, thereby increasing neuronal survival time and restoring astrocyte functions. Improvement in learning deficits was also demonstrated by D'Agostino et al. (2012), correlating the neuroprotective effect of PEA with its ability to act on the PPAR-α receptor, in addition to its capacity to reduce oxidative stress through intracerebroventricular

administration in mice [120]. *In vitro* studies also demonstrate the therapeutic potential of PEA in AD. Facchinetti et al. (2022) investigated the compound Co-ultraPEALut in a cellular model of Aβ 1-42 toxicity, confirming its anti-inflammatory activity, preventing astrocyte reactivity and reducing growth factor transcription induced by Aβ1-42 exposure, with these effects being correlated with the activation of PPAR-α receptors [121].

Furthermore, PEA improves intestinal motility dysfunction associated with AD by neutralizing proteins related to neurodegenerative disorders, Aβ, t-tau, and α-synuclein, as observed by D'Antongiovanni et al. (2021), in a mouse study through oral administration of PEA. PEA reduces citrate synthase activity (associated with premature aging) and neutralizes intestinal inflammation and enteric gliosis associated with cognitive decline [19]. Also, improves the integrity and permeability of the intestinal epithelial barrier by reducing the expression of pro-inflammatory cytokines such as calcium-binding protein B (S100-β), toll-like receptor 4 (TLR-4), and nuclear factor-κB p65 (NF-κBp65) [19].These actions demonstrate that PEA may be useful in the development of symptoms associated with AD.

5.1.3. Vascular Dementia

Vascular dementia or vascular cognitive impairment is characterized by chronic and acute cognitive impairment with deficits in memory, aphasia, apraxia, agnosia or executive dysfunction and impaired ability to perform daily activities [7]. It holds great importance in research and therapy development due to its epidemiology, being the second most common type of dementia, second only to Alzheimer's Disease [122]. The develop

ment of vascular dementia is correlated with obesity, insulin resistance, diabetes, hyperhomocysteinemia, hypertension, and hyperlipidemia, conditions that promote an inflammatory state in the body [122].

Impellizzeri et al. (2019) proposed the use of PEA-OXA in mice through oral administration, observing the neuroprotective effect increasing endogenous PEA levels in the brain, reducing the presence of injured neuronal cells in the hippocampus, apoptosis and immunoreactivity for GFAP and Iba-1 and increasing microtubule-associated protein 2

(MAP-2) expression [123]. Another effect of PEA-OXA administration was the ability to prevent IκB-α degradation, nuclear translocation of NF-κB and a reduction in iNOS and COX-2 expression. A very interesting factor, also demonstrated by Impellizzeri et al. (2019), was the ability of PEA to increase the levels of anti-inflammatory cytokines such as interleukin-10 (IL-10) and positively regulate the antioxidant response by acting on the nuclear factor erythroid 2-related factor 2 (Nrf-2) pathway, as well as improving cognitive deficits [123].

5.1.4. Multiple Sclerosis

Multiple sclerosis [110] is a non-traumatic disabling disease classified as an autoimmune disease and is common in adults and young individuals [124], exhibiting a heterogeneous symptomatology with distinct signs due to impairment of the motor, sensory, visual, and autonomic systems [125].

The inflammatory processes in MS are the main factor contributing to the development of lesions [124]. In this way, PEA has been studied for its anti-inflammatory characteristics. In an experimental autoimmune encephalomyelitis model, Contarini et al. (2019) demonstrated that PEA, in combination with ultramicronized luteolin (co-ultraPEA-LUT) administered intraperitoneally, improved the clinical severity in mice and reduced the inflammatory response by modulating the activity of serum amyloid A1 (SAA1), TNF-α, interferon-gamma (IFN-γ), and the NLRP3 inflammasome [20].

In summary, the therapeutic potential of PEA in the central nervous system encompasses various pathologies (Tables 2–4). In all of these conditions, PEA exerts an anti-inflammatory effect by modulating inflammatory mediators, reactive oxygen species, and transcription factors. In most cases, these effects occur via PPAR-type receptors, highlighting the importance of this pathway in the treatment of CNS pathologies.

5.2. Therapeutic Potential of PEA in Pain, Inflammatory Processes, and Immune System Modulation

In the mid-2000s, Italian researchers demonstrated the anti-inflammatory potential of PEA. This study conducted by Costa et al. (2002) assessed this effect following oral administration of PEA in rats. The authors reported a time-dependent reduction in edema, decreased COX activity, lowered levels of nitrite/nitrate (NO2− /NO3 −) and malondialdehyde [126]. Loverme et al. (2006) also showed a reduction in hyperalgesic responses due the anti-inflammatory effect of PEA, injected in the mice and rats paws, after an experimental model of sciatic nerve injury. The researchers observed that the effects were closely linked to the PEA action on the PPAR-α receptor [127]. D'Agostino et al. (2009) obtained similar results when investigating the therapeutic action of PEA in mice treated intracerebroventricularly in a paw edema model. PEA inhibited the expression of COX-2 and iNOS and prevented IkB-α degradation. The anti-hyperalgesic and anti-inflammatory actions of the PEA were mediated through the PPAR-α receptor [128].

The antinociceptive potential of PEA has been demonstrated in various experimental models. Romero and Duarte (2012) showed the antinociceptive effect of PEA, administered locally, in a Wistar rat model of hyperalgesia induced by intraplantar injection of PGE2. The lipid exerted a local peripheral antinociceptive effect, which the authors attributed to the activation of ATP-sensitive K(+) channels [129]. In another study by Romero et al. (2012), using the same rat model, local PEA administration resulted in the activation of the nitric oxide pathway, initiating the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) signaling pathway, which was associated with its antinociceptive potential [130]. And, in 2013, they observed the antinociceptive therapeutic effect of PEA through the activation of the CB2 receptor, resulting in the stimulation of endogenous norepinephrine release and the activation of peripheral α2 adrenoceptors [17]. Another interesting finding was demonstrated by Galdino et al. (2014), where plasma concentrations of PEA increased after acute resistance exercise in rats undergoing a weightlifting model. This discovery aligns with the antinociceptive action of PEA, due to an endogenous activation of the endocannabinoid system following intense exercise [131]. These studies demonstrate the ability of PEA to exert its antinociceptive therapeutic potential on multiple targets.

Siracusa et al. (2020) verified the effect of PEA on post-operative pain in rats, using micronized palmitoylethanolamide (PEA-um). After the rat paw injury, there was relief in mechanical allodynia, thermal hyperalgesia, and motor coordination. Pre and post-injury treatment reduced mast cell infiltration, NGF levels, p-ERK kinase expression, BDNF, NF-κB, and iNOS. Additionally, Siracusa et al. (2020) noted that PEA-um reduced microglial and mast cell activation [18].

Table 2. Main effects of Palmitoylethanolamide in experimental models of Nervous System pathologies.

	Pathological Condition	Experimental Model	Lineage	Gender	Age	Formulation	A.R.	Main effect	Receptor	Reference
	AD	Mice	3×Tg-AD	M	3 e 9m	PEA-um	s.c.	Neuroprotective and anti-inflammatory	-	[119]
	AD	Mice	SAMP8	**	4m	PEA	p.o.	Anti-inflammatory	-	[19]
	AD	Mice	**	**	**	PEA	icv	Neuroprotective	PPAR-α	[92]
	Multiple Sclerosis	Mice	C57BL/6	**	**	co-ultraPEA-Lut	i.p.	Anti-inflammatory and immunomodulator	-	[20]
	Anxiety associated to neuroinflammation	Mice	C57Bl/6J	M	6 w.	PEA	p.o.	Anti-inflammatory	PPAR-α	[115]
Nervous System	Neuroinflammation	Mice	C57BL/6J	M	10-12 w.	PEA	i.p.	Anti-inflammatory	PPAR-α	[116]
	Neuroinflammation	Mice	CD1	**	**	co-ultraPEALut	i.p.	Anti-inflammatory	PPARα e PPARβ	[117]
	Experimental spinal cord injury	Mice	CD1	M	Adult	PEA	i.p.	Anti-inflammatory and immunomodulator	PPARα	[104]
	Vascular dementia	Mice	CD2	M	**	PEA-OXA	p.o.	Neuroprotective	-	[123]
	Spinal Cord Injury	Mice	CD1	M	**	co-ultraPEALut	i.p.	Regeneration and immunomodulator	-	[105]
	Cerebral ischemia	Rat	Wistar	M	**	Co-ultraPEALut	i.v.	Anti-inflammatory and immunomodulator	-	[106]
	Focal cerebral ischemia	Rat	Wistar	M	**	PEA-OXA	i.v.	Anti-inflammatory and immunomodulator	-	[108]

Spinal Cord Injury	Mice	CD1	**	**	PEA	i.p.	Neuroprotective and anti-inflammatory	PPAR-δ PPAR-γ	[25]
Sciatic nerve injury	Mice	CD1	M	**	PEA-OXA	p.o.	Neuroprotective and anti-inflammatory	-	[21]
Sciatic nerve injury	Mice	Mutants	**	**	PEA	s.c.	Neuroprotective and anti-inflammatory	PPAR-α	[107]

(AD: Alzheimer's disease; M: male; W: weeks; M.: Months; PEA-um: Micronized Palmitoylethanolamide; co-ultraPEA-LUT: Ultramicronized Palmitoylethanolamide with Luteolin; PEA-OXA: Palmitoylethanolamine with oxametazoline; A.R.: administration routes; s.c.: Subcutaneous; p.o.: Oral; i.c.v.: Intracerebroventricular; i.p.: Intraperitoneal; i.v.: Intravenous).

Table 3. Main effects of Palmitoylethanolamide in in vitro models of Central Nervous System pathologies.

	Pathological condition	Experimental Model	Formulation	Cellular model	Main effect	Receptor	Reference
Central Nervous System	AD	*In vitro*	Co-ultra PEALut	Aβ 1-42toxicity	Anti-inflammatory	PPAR-α	[121]
	Neuroinflammation	*In vitro*	PEA	N9 microglial cells	Neuroprotective	CB$_2$	[114]
	Neuroinflammation	*In vitro*	PEA	Microglial astrocyte co-cultures	Neuroprotective	PPAR-α	[112]
	Neuroinflammation/ Neurodegeneration	*In vitro*	PEA	Astrocyte culture	Anti-inflammatory	PPAR-α	[113]

(AD: Alzheimer's Disease; co-ultraPEA-LUT: Ultramicronized Palmitoylethanolamide with Luteolin).

Table 4. Effect of Palmitoylethanolamide in patients with cerebral ischemia.

	Pathological condition	Clinical trial	Population	Age	Formulation	Dosage	Time	Main effect	Reference
Central Nervous System	Cerebral ischemia	Observational	Men and women	31–100 years old	co-ultraPEA-LUT (S.L.)	700mg+70 mg	2m	Clinical improvement	[106]

(S.L.: sublingual route; m: months; co-ultraPEA-LUT: Ultramicronized Palmitoylethanolamide with Luteolin).

The anti-inflammatory and anti-hyperalgesic activity of PEA was also observed in a rat paw edema model conducted by Petrosino et al. (2018) when administering PEA-um orally to the animals. The compound neutralized paw edema and thermal hyperalgesia, reduced neutrophil and mast cell infiltration, decreased the production of pro-inflammatory and pro-nociceptive cytokines such as TNF-α, IL-6, and IL-1β, as well as nitrate proteins and iNOS expression. Furthermore, Petrosino et al. (2018) also observed a reduction in COX-2 expression, degradation of IκB-α, and nuclear translocation of NF-κB p65 [72].

Considering the anti-inflammatory and analgesic effects of PEA, Peritore et al. (2020) evaluated the therapeutic potential of PEA-um in combination with Paracetamol to assess synergy between the molecules. They administered the compounds to rats in a sciatic nerve injury model. The authors observed anti-inflammatory and analgesic activities of the compound reducing edema and inflammatory infiltrates, including mast cell, and mechanical pain threshold, along with a significant reduction in the expression of c-Fos protein, NGF, TNF-α, and IL-1β [132]. The analgesic effect of PEA was correlated with its anti-inflammatory capacity, as observed by De Filippis et al. (2011) [133]. The authors assessed the analgesic profile in a model of chronic granulomatous inflammation induced in rats, finding that the compound inhibited mast cell degranulation, reduced NGF protein and mechanical allodynia, marked by reduced levels of TNF-α, NGF, and COX-2.

Another formulation proposed by Ardizzone et al. (2021) consists of PEA-um in combination with Acetyl-L-carnitine [134]. PEA-um was administered orally to potentiate the effects on neuropathic pain, in an experimental model of inflammatory pain in rats. The authors observed reduced inflammatory cell infiltration, decreased myeloperoxidase (MPO) enzyme activity, reduced course of thermal hyperalgesia, as well as mast cell numbers and the reduced expression of intercellular adhesion molecule 1 (ICAM-1). Additionally, Ardizzone et al. (2021) noted a reduction

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in IL-1β, COX-2 expression, and iNOS [134]. In a similar study, Seol et al. (2017) administered PEA-um intraperitoneally in rats. PEA-um reduced inflammatory and neuropathic pain providing relief from chronic inflammation-induced mechanical hyperalgesia [135].

In the same context, the synergic action of PEA-OXA was investigated by Petrosino et al. (2017) in neuropathic and inflammatory pain model. Through oral administration to rats and mice, PEA-OXA demonstrate anti-inflammatory and immunomodulatory properties. These therapeutic activities involve the ability to inhibit NAAA, reduce the course of edema and hyperalgesia, restore endogenous lipid levels such as 2-AG, AEA, and OEA, reduce neutrophil and mast cell infiltration, ICAM-1 expression, and the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [13]. Furthermore, Petrosino et al. (2017) also observed a reduction in the expression of IκB-α and nuclear translocation of NF-κBp65, as well as iNOS and COX-2, with therapeutic effects and immune system modulation linked to the activation of the PPAR-α receptor [13].

5.2.1. Osteoarthritis and Inflammatory Arthritis

Osteoarthritis is a chronic joint disease with a high prevalence in patients over 65 years of age, characterized by symptoms such as chronic pain, joint instability, stiffness, joint deformities, and radiographic narrowing of the joint space, affecting joints in the knees, hands, hips, and spine [136]. The primary treatment involves the use of analgesics; however, continuous use can result in adverse reactions such as gastric ulcers and bleeding [137].

A recent study from 2021 conducted by researchers in South Korea [138] demonstrated the absence of adverse effects of PEA in the treatment of osteoarthritis induced in rats. PEA not only reduced knee swelling but also improved cartilage degradation, reduced the loss of aggrecan proteoglycan, alleviated inflammation, as evidenced by a reduction in mRNA expression of iNOS, 5-Lox, COX-2, TNF-α, and IL-1β. Moreover, it modulated the expression of matrix metalloproteinases and tissue inhibitor of metalloproteinase (TIMP1).

Another interesting study, conducted by Impellizzeri et al. (2013), highlighted the use of co-ultraPEALut in the treatment of inflammatory arthritis induced in mice [139]. This compound reduced the development of the inflammatory process, alleviated hyperalgesia, attenuated mast cell degranulation and neutrophil infiltration, and reduced levels of TNF-α, IL-1β, and IL-6, as well as nitrotyrosine formation. It promoted an improvement in clinical signs and motor activity in the animals.

5.2.2. Hypersensitivity

Due to its anti-inflammatory and immunomodulatory potential, PEA can modify the degree of hypersensitivity in allergic conditions such as asthma. A study conducted by Roviezzo et al. (2017) demonstrated that PEA prevents hyperreactivity, blocks allergen-induced eosinophil extravasation, and is associated with its ability to prevent the increase of pro-inflammatory cytokines such as IL-4 and IL-13. Additionally, PEA attenuated lung inflammation and mast cell activity, as well as levels of Leukotriene C4 (LTC4), a key inflammatory mediator in allergic asthma [16] Table 5.

Table 5. Main effects of PEA on pain and inflammatory processes associated with arthritis and hypersensitivity reactions.

	Pathological Condition	Experimental Model	Lineage	Formulation	A.R.	Main Effect	Receptor	Reference
	Postoperative pain	Rat	Sprague-Dawley	PEA-um	p.o.	Anti-inflammatory and analgesic	-	[18]
	Sciatic nerve injury	Rat	Sprague-Dawley	PEAum-Paracetamol	p.o.	Anti-inflammatory and analgesic	-	[132]
Pain and inflammatory processes	Sciatic nerve injury	Mice and Rat	Swiss and Sprague-Dawley	PEA	i.pl.	Anti-inflammatory and analgesic	PPAR-α	[127]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	Canais de K$^{(+)}$	[129]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	nNOS	[130]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	CB$_2$	[17]

Paw edema	Rat	Sprague-Dawley	PEA-um	p.o.	Anti-hyperalgesic and anti-inflammatory	-	[72]
Paw edema	Rat	Sprague-Dawley	PEA-um and LAC	p.o.	Anti-inflammatory and analgesic	-	[134]
Paw edema	Mice	Swiss	PEA	i.c.v.	Anti-hyperalgesic and anti-inflammatory	PPAR-α	[92]
Inflammatory and neuropathic pain	Rat	Sprague-Dawley	PEA	i.p.	Anti-hyperalgesic and anti-inflammatory	-	[135]
Inflammatory and neuropathic pain	Mice and Rat	Sprague-Dawley and mutant mice	PEA-OXA	p.o.	Anti-inflammatory and immunomodulatory	PPAR-α.	[13]
Acute inflammation	Rat	Wistar	PEA	p.o.	Anti-inflammatory	-	[126]
Osteoarthritis	Rat	Sprague-Dawley	PEA	p.o.	Anti-inflammatory and immunomodulatory	-	[138]
Osteoarthritis	Mice	DBA	co-ultraPEALut	i.p.	Anti-inflammatory	-	[71]
Hypersensitivity	Mice	BALB/c	PEA	p.o.	Immunomodulatory	-	[16]
Chronic granulomatous inflammation	Rat	Wistar	PEA	s.c.	Anti-inflammatory and immunomodulatory	-	[133]

(M: male; F: female; W: weeks; D: days; PEA-um: Micronized Palmitoylethanolamide; co-ultraPEA-LUT: Ultramicronized Palmitoylethanolamide with Luteolin; PEA LAC: Palmitoylethanolamide Acetil-l-carnitina; PEA-OXA: Palmitoylethanolamide with oxametazoline; A.R.: Administration Routes; S.C: Subcutaneous; P.O.: Oral; I.C.V.: Intracerebroventricular; I.P.: Intraperitoneal; I.Pl: intraplantar; I.V.: Intravenous).

5.3. Therapeutic Potential of PEA in Vascular System Disorders

PEA has demonstrated therapeutic potential in disseminated intravascular coagulation (DIC), a disorder that promotes multisystem thrombus formation with a tendency for bleeding and organ dysfunction. D'Amico et al. (2021) addressed the use of micronized lipid compound through intravenous administration in rats, observing its anti-inflammatory and neuroprotective activity [140]. They found that PEA increased platelet count and fibrin concentration, while prothrombin time [110], activated partial thromboplastin time (aPTT), and plasma levels of D-dimer were significantly reduced. Confirming the data observed in other discussed studies, the authors stated that the anti-inflammatory activity is correlated with the modulation of plasma levels of IL-1β, IL-6, TNF-α, and IFN-γ, as well as reducing the degradation of IκB-α and, consequently, nuclear translocation of NF-κB. Another interesting aspect observed in the study by D'Amico et al. (2021) was the ability to reduce mast cell activation [140] Table 6.

5.4. Therapeutic Potential of PEA in Gastrointestinal Disorders

Wang et al. (2014) and their research group demonstrated the ability of PEA to exert anti-inflammatory activity in a radiation-induced intestinal inflammation model. This study also observed an improvement in the lesion site, including a reduction in overall radiation-induced structural damage, intestinal wall thickness, collagen deposition, and neutrophil influx in irradiated intestinal areas. In addition, Wang et al. (2014) observed that the compound inhibited pathways controlling mast cell-derived cellular immune systems, anti-inflammatory signaling of IL-6 and IL-10, and activated the prothrombin pathway. It is interesting to note that in mice with immune system deficiencies, the effect of PEA was contrary; it suppressed non-mast cell-derived immune responses, increased anti-inflammatory signaling of IL-10 and IL-6, and decreased prothrombin pathway activation [141].

Recent studies have also shown positive results in the context of colitis, i.e., intestinal inflammation. Borrelli et al. (2015) demonstrated the anti-inflammatory potential of PEA in an experimental mouse model, which resulted in reduced edema and erosion areas, leukocyte infiltration, intestinal permeability, and stimulated colonic cell regeneration. According to the authors, these activities involved the action on CB2, GPR55, and PPARα receptors [68].

Another similar study involving colitis was conducted by Peritore et al. (2021), but the authors used the compound PEA/Pol-co, which combines palmitoylethanolamide with polydatin, a derivative of fatty acid. This molecule was tested in mice, and the authors observed anti-inflammatory activity, improved clinical signs, reduced pro-inflammatory cytokines IL-1β and TNF-

α, myeloperoxidase (MPO), malondialdehyde (MDA), nitrotyrosine expression, PARP protein, ICAM-1, and P-selectin, as well as increased levels of SIRT-1, heme oxygenase 1 (HO-1) expression, and Nrf2 [142].

The anti-inflammatory effect of PEA-OXA was also observed in an experimental zebrafish model of colitis, as proposed by Di Paola et al. (2022) [63]. The compound was found to reduce intestinal damage, mucus production, and the expression of inflammatory and endoplasmic reticulum stress-related genes.

The role of PEA in the digestive system was demonstrated by Hu et al. (2021) in a mouse model of non-alcoholic steatohepatitis (NASH) [143]. Non-alcoholic steatohepatitis is a chronic liver disease with a wide range of symptoms, including hepatic steatosis, inflammation, ballooning, and fibrosis, with a high risk of progressing to hepatocellular carcinoma [144].

Hu et al. (2021) observed that PEA significantly attenuated the progression of non-alcoholic steatohepatitis, relieved oxidative stress, reduced gene expression related to li

pid metabolism, such as mRNA of acetyl-CoA carboxylase 1 (ACC1) and CD36, and mitigated inflammatory mediators such as MPO, iNOS, TNF-α, chemokine ligand 5 (CCL5), monocyte chemoattractant protein-1 (MCP-1), also inhibiting the activation of the NLRP3 inflammasome. Another interesting aspect observed by the research group was the ability of PEA to increase PPAR-α mRNA and protein [143] Table 6.

5.5. Therapeutic Potential of PEA in Respiratory Disorders

Studies addressing the role of PEA in the respiratory system are quite recent and have shown concern regarding exacerbated inflammatory responses, especially in the context of COVID-19, as proposed by Peritore et al. (2021) Table 6. The authors investigated the role of micronized PEA (um-PEA) in an animal model of acute lung injury, demonstrating that the compound has the ability to reduce lung injury by decreasing neutrophil responses, mast cell recruitment to the lungs, and modulation of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, and IL-18 [142]. Another interesting aspect observed in the study by Peritore et al. (2021) was the ability of PEA to act on different inflammatory pathways, managing the pERK, pJNK, p38MAPK, and NF-kB pathways [142].

Similar results were observed in a clinical observational case-control study involving patients with early-stage COVID-19. The study conducted by Albanese et al. (2022) included both men and women aged 18 to 80, who were treated with a daily dose of 1880 mg for 28 days. The authors highlight the anti-inflammatory and modulatory effects of the compound due to its role in reducing the inflammatory state and oxidative stress, as well as promoting changes in the coagulation cascade [145] Table 7.

Table 6. Therapeutic effects of PEA in the management of diseases related to the gastrointestinal system, vascular system, digestive system and respiratory system.

	Pathological Condition	Experimental Model	Lineage	Formulation	A.R.	Main Effect	Receptor	Reference
	Intestinal inflammation	Rat	Mutants	PEA	i.v.	Anti-inflammatory and immunomodulator	-	[141]
Gastrointestinal System	Colitis	Mice	ICR	PEA	p.o.	Anti-inflammatory	TRPV1 e CB$_1$	[49]
	Colitis	Mice	CD1	PEA-um + Paracetamol	p.o.	Anti-inflammatory	-	[132]
	Inflammatory bowel disease	Zebrafish Larvae	Wild (WT)	PEA-OXA	**	Anti-inflammatory	-	[63]
Vascular System	Coagulopathy	Rat	Sprague-Dawley	PEA-um	p.o.	Anti-inflammatory and neuroprotective	-	[140]
Digestive system	Steatohepatitis	Mice	C57BL/6	PEA	p.o.	Antii-inflamatório	PPAR-α	[143]
Respiratory system	Acute lung injury	Mice	CD1	PEA-um	p.o	Anti-inflammatory and immunomodulator	-	[142]

M: male; m.: Months; PEA-um: Micronized Palmitoylethanolamide; PEA-OXA: Palmitoylethanolamine with oxametazoline; A.R.: admi istration routes; p.o.: Oral; i.v.: Intravenous).

Table 7. Effect of PEA on patients with COVID-19.

Pathological Condition	Clinical trial	Gender	Age	Formulation	A.R.	Dosage	Time	Main Effect	Reference
Respiratory system	COVID-19	Case-control	Men and women	18-80 years old	PEA-um	o.p.	1800 mg	28d	Anti-inflammatory and immunomodulator	[145]

PEA-um: Micronized Palmitoylethanolamide; A.R.: administration routes; p.o.: Oral.

6. Conclusions

The endocannabinoid system has a widespread distribution in the human body, and its multitude of actions, targets, and ligands can be useful in the treatment of various diseases and the development of new therapies. Palmitoylethanolamide (PEA) is an endocannabinoid-like compound that has been the subject of numerous studies, involving its role in various systems and diseases, such as the central nervous system, immune system, vascular system, digestive system, and respiratory system. This literature review identified a diversity of studies on the properties of PEA with approaches in clinical studies, animal and human experimental models, and *in vitro* studies. PEA was used either alone or in combination with other active compounds, such as luteolin, paracetamol, or oxazoline, to potentiate its effects, leading to interesting synergistic effects, such as enhanced analgesic effects in post-surgical pain. PEA demonstrated effectiveness in Alzheimer's disease, Multiple Sclerosis, neuroinflammation, cerebral ischemia, vascular dementia, inflammatory conditions such as arthritis, neuropathic pain, hypersensitivity, colitis, inflammatory bowel disease, acute lung injury, coagulopathy, and non-alcoholic steatohepatitis. Its action is particularly prominent on PPARα receptors, but there are also reports of its activity mediated by PPAR-δ and PPAR-γ, CB1, CB2, GPR55, and TRPV1 receptors. Furthermore, the studies reviewed in this article show a significant potential for PEA to modulate events in the inflammatory cascade and have a direct impact on immune response modulation. However, clinical findings in humans are limited, leaving a gap in knowledge regarding adverse events, safety profiles, and effectiveness. Therefore, despite PEA showing promising results in animal experimental models, it is premature to conclude that similar outcomes would be observed in humans. Clinical studies are needed to evaluate the therapeutic potential of PEA, mainly to treat inflammatory and immune disorders.

References

1. Pertwee, R.G., *Endocannabinoids and Their Pharmacological Actions.* Handb Exp Pharmacol, 2015. **231**: p. 1-37.
2. Devane, W.A., et al., *Isolation and structure of a brain constituent that binds to the cannabinoid receptor.* Science, 1992. **258**(5090): p. 1946-9.
3. Hanus, L., et al., *2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor.* Proc Natl Acad Sci U S A, 2001. **98**(7): p. 3662-5.
4. Porter, A.C., et al., *Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor.* J Pharmacol Exp Ther, 2002. **301**(3): p. 1020-4.
5. Huang, S.M., et al., *An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors.* Proc Natl Acad Sci U S A, 2002. **99**(12): p. 8400-5.
6. Cascio, M.G., *PUFA-derived endocannabinoids: an overview.* Proc Nutr Soc, 2013. **72**(4): p. 451-9.
7. Engelhardt, E., et al., *Vascular dementia: Diagnostic criteria and supplementary exams. Recommendations of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology. Part I.* Dement Neuropsychol, 2011. **5**(4): p. 251-263.
8. Maccarrone, M. and A. Finazzi-Agro, *Endocannabinoids and their actions.* Vitam Horm, 2002. **65**: p. 225-55.

9.   Coburn, A.F., C.E. Graham, and J. Haninger, *The effect of egg yolk in diets on anaphylactic arthritis (passive Arthus phenomenon) in the guinea pig.* J Exp Med, 1954. **100**(5): p. 425-35.

10.   Ganley, O.H., O.E. Graessle, and H.J. Robinson, *Anti-inflammatory activity on compounds obtained from egg yolk, peanut oil, and soybean lecithin.* J Lab Clin Med, 1958. **51**(5): p. 709-14.

11.   Gugliandolo, E., et al., *Dietary Supplementation with Palmitoyl-Glucosamine Co-Micronized with Curcumin Relieves Osteoarthritis Pain and Benefits Joint Mobility.* Animals (Basel), 2020. **10**(10).

12.   Bruun, S., et al., *Satiety Factors Oleoylethanolamide, Stearoylethanolamide, and Palmitoylethanolamide in Mother's Milk Are Strongly Associated with Infant Weight at Four Months of Age-Data from the Odense Child Cohort.* Nutrients, 2018. **10**(11).

13.   Petrosino, S. and V. Di Marzo, *The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations.* Br J Pharmacol, 2017. **174**(11): p. 1349-1365.

14.   Okamoto, Y., et al., *Molecular characterization of a phospholipase D generating anandamide and its congeners.* J Biol Chem, 2004. **279**(7): p. 5298-305.

15.   Perlik, F., H. Raskova, and J. Elis, *Anti-inflammatory properties of N(2-hydroxyethyl) palmitamide.* Acta Physiol Acad Sci Hung, 1971. **39**(4): p. 395-400.

16.   Roviezzo, F., et al., *Palmitoylethanolamide Supplementation during Sensitization Prevents Airway Allergic Symptoms in the Mouse.* Front Pharmacol, 2017. **8**: p. 857.

17.   Romero, T.R., et al., *CB1 and CB2 cannabinoid receptor agonists induce peripheral antinociception by activation of the endogenous noradrenergic system.* Anesth Analg, 2013. **116**(2): p. 463-72.

18.   Siracusa, R., et al., *The Protective Effects of Pre- and Post-Administration of Micronized Palmitoylethanolamide Formulation on Postoperative Pain in Rats.* Int J Mol Sci, 2020. **21**(20).

19.   D'Antongiovanni, V., et al., *Palmitoylethanolamide Counteracts Enteric Inflammation and Bowel Motor Dysfunctions in a Mouse Model of Alzheimer's Disease.* Front Pharmacol, 2021. **12**: p. 748021.

20.   Contarini, G., et al., *A co-ultramicronized palmitoylethanolamide/luteolin composite mitigates clinical score and disease-relevant molecular markers in a mouse model of experimental autoimmune encephalomyelitis.* J Neuroinflammation, 2019. **16**(1): p. 126.

21.   Gugliandolo, E., et al., *Effect of PEA-OXA on neuropathic pain and functional recovery after sciatic nerve crush.* J Neuroinflammation, 2018. **15**(1): p. 264.

22.   Clayton, P., et al., *Palmitoylethanolamide: A Natural Compound for Health Management.* Int J Mol Sci, 2021. **22**(10).

23.   Iannotti, F.A., V. Di Marzo, and S. Petrosino, *Endocannabinoids and endocannabinoid-related mediators: Targets, metabolism and role in neurological disorders.* Prog Lipid Res, 2016. **62**: p. 107-28.

24.   Aloe, L., A. Leon, and R. Levi-Montalcini, *A proposed autacoid mechanism controlling mastocyte behaviour.* Agents Actions, 1993. **39 Spec No**: p. C145-7.

25.   Paterniti, I., et al., *Molecular evidence for the involvement of PPAR-delta and PPAR-gamma in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma.* J Neuroinflammation, 2013. **10**: p. 20.

26.   Neher, M.D., et al., *New insights into the role of peroxisome proliferator-activated receptors in regulating the inflammatory response after tissue injury.* PPAR Res, 2012. **2012**: p. 728461.

27.   Im, D.S., *GPR119 and GPR55 as Receptors for Fatty Acid Ethanolamides, Oleoylethanolamide and Palmitoylethanolamide.* Int J Mol Sci, 2021. **22**(3).

28.   Mechoulam, R., E. Fride, and V. Di Marzo, *Endocannabinoids.* Eur J Pharmacol, 1998. **359**(1): p. 1-18.

29.   Mechoulam, R. and Y. Gaoni, *A Total Synthesis of Dl-Delta-1-Tetrahydrocannabinol, the Active Constituent of Hashish.* J Am Chem Soc, 1965. **87**: p. 3273-5.

30.   Howlett, A.C., B.F. Thomas, and J.W. Huffman, *The Spicy Story of Cannabimimetic Indoles.* Molecules, 2021. **26**(20).

31.   Munro, S., K.L. Thomas, and M. Abu-Shaar, *Molecular characterization of a peripheral receptor for cannabinoids.* Nature, 1993. **365**(6441): p. 61-5.

32.   Di Marzo, V., M. Bifulco, and L. De Petrocellis, *The endocannabinoid system and its therapeutic exploitation.* Nat Rev Drug Discov, 2004. **3**(9): p. 771-84.

33.   Yang, F. and J. Zheng, *Understand spiciness: mechanism of TRPV1 channel activation by capsaicin.* Protein Cell, 2017. **8**(3): p. 169-177.

34.   O'Sullivan, S.E., *An update on PPAR activation by cannabinoids.* Br J Pharmacol, 2016. **173**(12): p. 1899-910.

35.   Galiegue, S., et al., *Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations.* Eur J Biochem, 1995. **232**(1): p. 54-61.

36.   Howlett, A.C., *Pharmacology of cannabinoid receptors.* Annu Rev Pharmacol Toxicol, 1995. **35**: p. 607-34.

37.   Castillo, P.E., et al., *Endocannabinoid signaling and synaptic function.* Neuron, 2012. **76**(1): p. 70-81.

38. Brown, S.P., S.D. Brenowitz, and W.G. Regehr, *Brief presynaptic bursts evoke synapse-specific retrograde inhibition mediated by endogenous cannabinoids.* Nat Neurosci, 2003. **6**(10): p. 1048-57.

39. Kreitzer, A.C. and W.G. Regehr, *Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells.* Neuron, 2001. **29**(3): p. 717-27.

40. Wilson, R.I., G. Kunos, and R.A. Nicoll, *Presynaptic specificity of endocannabinoid signaling in the hippocampus.* Neuron, 2001. **31**(3): p. 453-62.

41. Chevaleyre, V., K.A. Takahashi, and P.E. Castillo, *Endocannabinoid-mediated synaptic plasticity in the CNS.* Annu Rev Neurosci, 2006. **29**: p. 37-76.

42. Heifets, B.D. and P.E. Castillo, *Endocannabinoid signaling and long-term synaptic plasticity.* Annu Rev Physiol, 2009. **71**: p. 283-306.

43. Kano, M., et al., *Endocannabinoid-mediated control of synaptic transmission.* Physiol Rev, 2009. **89**(1): p. 309-80.

44. Ohno-Shosaku, T. and M. Kano, *Endocannabinoid-mediated retrograde modulation of synaptic transmission.* Curr Opin Neurobiol, 2014. **29**: p. 1-8.

45. Di Marzo, V. and F. Piscitelli, *The Endocannabinoid System and its Modulation by Phytocannabinoids.* Neurotherapeutics, 2015. **12**(4): p. 692-8.

46. Brown, A.J., *Novel cannabinoid receptors.* Br J Pharmacol, 2007. **152**(5): p. 567-75.

47. Bonilla, F.A. and H.C. Oettgen, *Adaptive immunity.* J Allergy Clin Immunol, 2010. **125**(2 Suppl 2): p. S33-40.

48. Holzer, P., *TRPV1 and the gut: from a tasty receptor for a painful vanilloid to a key player in hyperalgesia.* Eur J Pharmacol, 2004. **500**(1-3): p. 231-41.

49. Borrelli, F. and A.A. Izzo, *Role of acylethanolamides in the gastrointestinal tract with special reference to food intake and energy balance.* Best Pract Res Clin Endocrinol Metab, 2009. **23**(1): p. 33-49.

50. Grygiel-Gorniak, B., *Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications--a review.* Nutr J, 2014. **13**: p. 17.

51. O'Sullivan, S.E. and D.A. Kendall, *Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease.* Immunobiology, 2010. **215**(8): p. 611-6.

52. Delerive, P., J.C. Fruchart, and B. Staels, *Peroxisome proliferator-activated receptors in inflammation control.* J Endocrinol, 2001. **169**(3): p. 453-9.

53. Devchand, P.R., et al., *The PPARalpha-leukotriene B4 pathway to inflammation control.* Nature, 1996. **384**(6604): p. 39-43.

54. Cai, W., et al., *Peroxisome proliferator-activated receptor gamma (PPARgamma): A master gatekeeper in CNS injury and repair.* Prog Neurobiol, 2018. **163-164**: p. 27-58.

55. Kadayat, T.M., et al., *Targeting Peroxisome Proliferator-Activated Receptor Delta (PPARdelta): A Medicinal Chemistry Perspective.* J Med Chem, 2020. **63**(18): p. 10109-10134.

56. Grabacka, M., et al., *The Role of PPAR Alpha in the Modulation of Innate Immunity.* Int J Mol Sci, 2021. **22**(19).

57. Delerive, P., et al., *Induction of IkappaBalpha expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor-alpha activators.* J Biol Chem, 2000. **275**(47): p. 36703-7.

58. Calebiro, D. and A. Godbole, *Internalization of G-protein-coupled receptors: Implication in receptor function, physiology and diseases.* Best Pract Res Clin Endocrinol Metab, 2018. **32**(2): p. 83-91.

59. Godlewski, G., et al., *Receptors for acylethanolamides-GPR55 and GPR119.* Prostaglandins Other Lipid Mediat, 2009. **89**(3-4): p. 105-11.

60. Ryberg, E., et al., *The orphan receptor GPR55 is a novel cannabinoid receptor.* Br J Pharmacol, 2007. **152**(7): p. 1092-101.

61. Bachur, N.R., et al., *Fatty Acid Amides of Ethanolamine in Mammalian Tissues.* J Biol Chem, 1965. **240**: p. 1019-24.

62. Lambert, D.M., et al., *The palmitoylethanolamide family: a new class of anti-inflammatory agents?* Curr Med Chem, 2002. **9**(6): p. 663-74.

63. Di Paola, D., et al., *Intestinal Disorder in Zebrafish Larvae (Danio rerio): The Protective Action of N-Palmitoylethanolamide-oxazoline.* Life (Basel), 2022. **12**(1).

64. Cravatt, B.F., et al., *Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides.* Nature, 1996. **384**(6604): p. 83-7.

65. Clayton, P., et al., *Palmitoylethanolamide: A Potential Alternative to Cannabidiol.* J Diet Suppl, 2023. **20**(3): p. 505-530.

66. Smart, D., et al., *'Entourage' effects of N-acyl ethanolamines at human vanilloid receptors. Comparison of effects upon anandamide-induced vanilloid receptor activation and upon anandamide metabolism.* Br J Pharmacol, 2002. **136**(3): p. 452-8.

67. Kaplan, B.L., et al., *2-Arachidonoyl-glycerol suppresses interferon-gamma production in phorbol ester/ionomycin-activated mouse splenocytes independent of CB1 or CB2.* J Leukoc Biol, 2005. **77**(6): p. 966-74.

68. Borrelli, F., et al., *Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent.* Br J Pharmacol, 2015. **172**(1): p. 142-58.

69. Rankin, L. and C.J. Fowler, *The Basal Pharmacology of Palmitoylethanolamide.* Int J Mol Sci, 2020. **21**(21).

70. Tronino, D., et al., *Nanoparticles prolong N-palmitoylethanolamide anti-inflammatory and analgesic effects in vivo.* Colloids Surf B Biointerfaces, 2016. **141**: p. 311-317.

71. Impellizzeri, D., et al., *Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain.* J Neuroinflammation, 2014. **11**: p. 136.

72. Petrosino, S., et al., *Oral Ultramicronized Palmitoylethanolamide: Plasma and Tissue Levels and Spinal Anti-hyperalgesic Effect.* Front Pharmacol, 2018. **9**: p. 249.

73. Petrosino, S., et al., *The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels.* Br J Pharmacol, 2016. **173**(7): p. 1154-62.

74. Gabrielsson, L., S. Mattsson, and C.J. Fowler, *Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy.* Br J Clin Pharmacol, 2016. **82**(4): p. 932-42.

75. Zhukov, O.D., *[Distribution of N-([1-14C]-palmitoyl)ethanolamine in rat tissues].* Ukr Biokhim Zh (1999), 1999. **71**(4): p. 124-5.

76. Artamonov, M., et al., *Incorporation of labelled N-acylethanolamine (NAE) into rat brain regions in vivo and adaptive properties of saturated NAE under x-ray irradiation.* Ukr Biokhim Zh (1999), 2005. **77**(6): p. 51-62.

77. Svobodova, A., et al., *Distribution of an analgesic palmitoylethanolamide and other N-acylethanolamines in human placental membranes.* PLoS One, 2023. **18**(1): p. e0279863.

78. Schmid, P.C., M.L. Zuzarte-Augustin, and H.H. Schmid, *Properties of rat liver N-acylethanolamine amidohydrolase.* J Biol Chem, 1985. **260**(26): p. 14145-9.

79. Cravatt, B.F. and A.H. Lichtman, *The enzymatic inactivation of the fatty acid amide class of signaling lipids.* Chem Phys Lipids, 2002. **121**(1-2): p. 135-48.

80. Mattace Raso, G., et al., *N-Palmitoylethanolamide protects the kidney from hypertensive injury in spontaneously hypertensive rats via inhibition of oxidative stress.* Pharmacol Res, 2013. **76**: p. 67-76.

81. Petrosino, S., T. Iuvone, and V. Di Marzo, *N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities.* Biochimie, 2010. **92**(6): p. 724-7.

82. Mazzari, S., et al., *N-(2-hydroxyethyl)hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation.* Eur J Pharmacol, 1996. **300**(3): p. 227-36.

83. Scarampella, F., F. Abramo, and C. Noli, *Clinical and histological evaluation of an analogue of palmitoylethanolamide, PLR 120 (comicronized Palmidrol INN) in cats with eosinophilic granuloma and eosinophilic plaque: a pilot study.* Vet Dermatol, 2001. **12**(1): p. 29-39.

84. Theodosiou, M., et al., *Hyperalgesia due to nerve damage: role of nerve growth factor.* Pain, 1999. **81**(3): p. 245-255.

85. Lambert, D.M. and V. Di Marzo, *The palmitoylethanolamide and oleamide enigmas : are these two fatty acid amides cannabimimetic?* Curr Med Chem, 1999. **6**(8): p. 757-73.

86. Ho, W.S., D.A. Barrett, and M.D. Randall, *'Entourage' effects of N-palmitoylethanolamide and N-oleoylethanolamide on vasorelaxation to anandamide occur through TRPV1 receptors.* Br J Pharmacol, 2008. **155**(6): p. 837-46.

87. Del Re, A., et al., *Oral Adelmidrol Administration Up-Regulates Palmitoylethanolamide Production in Mice Colon and Duodenum through a PPAR-gamma Independent Action.* Metabolites, 2022. **12**(5).

88. De Petrocellis, L., et al., *Effect on cancer cell proliferation of palmitoylethanolamide, a fatty acid amide interacting with both the cannabinoid and vanilloid signalling systems.* Fundam Clin Pharmacol, 2002. **16**(4): p. 297-302.

89. Ambrosino, P., et al., *Activation and desensitization of TRPV1 channels in sensory neurons by the PPARalpha agonist palmitoylethanolamide.* Br J Pharmacol, 2013. **168**(6): p. 1430-44.

90. Capasso, R., et al., *Palmitoylethanolamide normalizes intestinal motility in a model of post-inflammatory accelerated transit: involvement of CB(1) receptors and TRPV1 channels.* Br J Pharmacol, 2014. **171**(17): p. 4026-37.

91. Deciga-Campos, M., et al., *N-palmitoylethanolamide synergizes the antinociception of morphine and gabapentin in the formalin test in mice.* J Pharm Pharmacol, 2023. **75**(9): p. 1154-1162.

92. D'Agostino, G., et al., *Acute intracerebroventricular administration of palmitoylethanolamide, an endogenous peroxisome proliferator-activated receptor-alpha agonist, modulates carrageenan-induced paw edema in mice.* J Pharmacol Exp Ther, 2007. **322**(3): p. 1137-43.

93. Annunziata, C., et al., *Palmitoylethanolamide Promotes White-to-Beige Conversion and Metabolic Reprogramming of Adipocytes: Contribution of PPAR-alpha.* Pharmaceutics, 2022. **14**(2).

94. Ye, S., et al., *PPARalpha-Dependent Effects of Palmitoylethanolamide Against Retinal Neovascularization and Fibrosis.* Invest Ophthalmol Vis Sci, 2020. **61**(4): p. 15.

95. Deciga-Campos, M., P.M. Ramirez-Marin, and F.J. Lopez-Munoz, *Synergistic antinociceptive interaction between palmitoylethanolamide and tramadol in the mouse formalin test.* Eur J Pharmacol, 2015. **765**: p. 68-74.

96. Pagano, E., et al., *Palmitoylethanolamide Reduces Colon Cancer Cell Proliferation and Migration, Influences Tumor Cell Cycle and Exerts In Vivo Chemopreventive Effects.* Cancers (Basel), 2021. **13**(8).

97. Avagliano, C., et al., *Palmitoylethanolamide protects mice against 6-OHDA-induced neurotoxicity and endoplasmic reticulum stress: In vivo and in vitro evidence.* Pharmacol Res, 2016. **113**(Pt A): p. 276-289.

98. Scuderi, C., et al., *Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices via peroxisome proliferator-activated receptor-alpha.* J Neuroinflammation, 2012. **9**: p. 49.

99. Cristiano, C., et al., *Palmitoylethanolamide counteracts autistic-like behaviours in BTBR T+tf/J mice: Contribution of central and peripheral mechanisms.* Brain Behav Immun, 2018. **74**: p. 166-175.

100. Guida, F., et al., *Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor.* Sci Rep, 2017. **7**(1): p. 375.

101. Rinne, P., et al., *Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation.* Arterioscler Thromb Vasc Biol, 2018. **38**(11): p. 2562-2575.

102. Marichal-Cancino, B.A., et al., *Potential Mechanisms Involved in Palmitoylethanolamide-Induced Vasodepressor Effects in Rats.* J Vasc Res, 2020. **57**(3): p. 152-163.

103. Kumar, A., et al., *Effects of palmitoylethanolamide on aqueous humor outflow.* Invest Ophthalmol Vis Sci, 2012. **53**(8): p. 4416-25.

104. Genovese, T., et al., *Effects of palmitoylethanolamide on signaling pathways implicated in the development of spinal cord injury.* J Pharmacol Exp Ther, 2008. **326**(1): p. 12-23.

105. Crupi, R., et al., *Co-Ultramicronized Palmitoylethanolamide/Luteolin Promotes Neuronal Regeneration after Spinal Cord Injury.* Front Pharmacol, 2016. **7**: p. 47.

106. Caltagirone, C., et al., *Co-ultramicronized Palmitoylethanolamide/Luteolin in the Treatment of Cerebral Ischemia: from Rodent to Man.* Transl Stroke Res, 2016. **7**(1): p. 54-69.

107. Di Cesare Mannelli, L., et al., *Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR-alpha-mediated mechanism.* Mediators Inflamm, 2013. **2013**: p. 328797.

108. Fusco, R., et al., *N-Palmitoylethanolamide-Oxazoline Protects against Middle Cerebral Artery Occlusion Injury in Diabetic Rats by Regulating the SIRT1 Pathway.* Int J Mol Sci, 2019. **20**(19).

109. DiSabato, D.J., N. Quan, and J.P. Godbout, *Neuroinflammation: the devil is in the details.* J Neurochem, 2016. **139 Suppl 2**(Suppl 2): p. 136-153.

110. Mechoulam, R., et al., *Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors.* Biochem Pharmacol, 1995. **50**(1): p. 83-90.

111. Lyman, M., et al., *Neuroinflammation: the role and consequences.* Neurosci Res, 2014. **79**: p. 1-12.

112. Hohmann, U., et al., *Opposite Effects of Neuroprotective Cannabinoids, Palmitoylethanolamide, and 2-Arachidonoylglycerol on Function and Morphology of Microglia.* Front Neurosci, 2019. **13**: p. 1180.

113. Scuderi, C., et al., *Palmitoylethanolamide counteracts reactive astrogliosis induced by beta-amyloid peptide.* J Cell Mol Med, 2011. **15**(12): p. 2664-74.

114. D'Aloia, A., et al., *Palmitoylethanolamide Modulation of Microglia Activation: Characterization of Mechanisms of Action and Implication for Its Neuroprotective Effects.* Int J Mol Sci, 2021. **22**(6).

115. Lama, A., et al., *Palmitoylethanolamide dampens neuroinflammation and anxiety-like behavior in obese mice.* Brain Behav Immun, 2022. **102**: p. 110-123.

116. Zhou, G., et al., *Palmitoylethanolamide ameliorates neuroinflammation via modulating PPAR-alpha to promote the functional outcome after intracerebral hemorrhage.* Neurosci Lett, 2022. **781**: p. 136648.

117. Paterniti, I., et al., *A new co-ultramicronized composite including palmitoylethanolamide and luteolin to prevent neuroinflammation in spinal cord injury.* J Neuroinflammation, 2013. **10**: p. 91.

118. Lane, C.A., J. Hardy, and J.M. Schott, *Alzheimer's disease.* Eur J Neurol, 2018. **25**(1): p. 59-70.

119. Scuderi, C., et al., *Ultramicronized palmitoylethanolamide rescues learning and memory impairments in a triple transgenic mouse model of Alzheimer's disease by exerting anti-inflammatory and neuroprotective effects.* Transl Psychiatry, 2018. **8**(1): p. 32.

120. D'Agostino, G., et al., *Palmitoylethanolamide protects against the amyloid-beta25-35-induced learning and memory impairment in mice, an experimental model of Alzheimer disease.* Neuropsychopharmacology, 2012. **37**(7): p. 1784-92.

121. Facchinetti, R., et al., *Co-Ultramicronized Palmitoylethanolamide/Luteolin Restores Oligodendrocyte Homeostasis via Peroxisome Proliferator-Activated Receptor-alpha in an In Vitro Model of Alzheimer's Disease.* Biomedicines, 2022. **10**(6).

122. Craft, S., *The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged.* Arch Neurol, 2009. **66**(3): p. 300-5.

123. Impellizzeri, D., et al., *N-Palmitoylethanolamine-oxazoline (PEA-OXA): A new therapeutic strategy to reduce neuroinflammation, oxidative stress associated to vascular dementia in an experimental model of repeated bilateral common carotid arteries occlusion.* Neurobiol Dis, 2019. **125**: p. 77-91.

124. Dobson, R. and G. Giovannoni, *Multiple sclerosis - a review.* Eur J Neurol, 2019. **26**(1): p. 27-40.

125. Doshi, A. and J. Chataway, *Multiple sclerosis, a treatable disease.* Clin Med (Lond), 2017. **17**(6): p. 530-536.

126. Costa, B., et al., *Therapeutic effect of the endogenous fatty acid amide, palmitoylethanolamide, in rat acute inflammation: inhibition of nitric oxide and cyclo-oxygenase systems.* Br J Pharmacol, 2002. **137**(4): p. 413-20.

127. LoVerme, J., et al., *Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-alpha.* J Pharmacol Exp Ther, 2006. **319**(3): p. 1051-61.

128. D'Agostino, G., et al., *Central administration of palmitoylethanolamide reduces hyperalgesia in mice via inhibition of NF-kappaB nuclear signalling in dorsal root ganglia.* Eur J Pharmacol, 2009. **613**(1-3): p. 54-9.

129. Romero, T.R. and I.D. Duarte, *N-palmitoyl-ethanolamine (PEA) induces peripheral antinociceptive effect by ATP-sensitive K+-channel activation.* J Pharmacol Sci, 2012. **118**(2): p. 156-60.

130. Romero, T.R., et al., *Involvement of the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway in peripheral antinociception induced by N-palmitoyl-ethanolamine in rats.* J Neurosci Res, 2012. **90**(7): p. 1474-9.

131. Galdino, G., et al., *Acute resistance exercise induces antinociception by activation of the endocannabinoid system in rats.* Anesth Analg, 2014. **119**(3): p. 702-715.

132. Peritore, A.F., et al., *Ultramicronized Palmitoylethanolamide and Paracetamol, a New Association to Relieve Hyperalgesia and Pain in a Sciatic Nerve Injury Model in Rat.* Int J Mol Sci, 2020. **21**(10).

133. De Filippis, D., et al., *Palmitoylethanolamide reduces granuloma-induced hyperalgesia by modulation of mast cell activation in rats.* Mol Pain, 2011. **7**: p. 3.

134. Ardizzone, A., et al., *Effect of Ultra-Micronized-Palmitoylethanolamide and Acetyl-l-Carnitine on Experimental Model of Inflammatory Pain.* Int J Mol Sci, 2021. **22**(4).

135. Seol, T.K., et al., *Effect of palmitoylethanolamide on inflammatory and neuropathic pain in rats.* Korean J Anesthesiol, 2017. **70**(5): p. 561-566.

136. Xia, B., et al., *Osteoarthritis pathogenesis: a review of molecular mechanisms.* Calcif Tissue Int, 2014. **95**(6): p. 495-505.

137. Hinz, B. and K. Brune, *Pain and osteoarthritis: new drugs and mechanisms.* Curr Opin Rheumatol, 2004. **16**(5): p. 628-33.

138. Jung, J.I., et al., *Anti-inflammatory activity of palmitoylethanolamide ameliorates osteoarthritis induced by monosodium iodoacetate in Sprague-Dawley rats.* Inflammopharmacology, 2021. **29**(5): p. 1475-1486.

139. Impellizzeri, D., et al., *Palmitoylethanolamide and luteolin ameliorate development of arthritis caused by injection of collagen type II in mice.* Arthritis Res Ther, 2013. **15**(6): p. R192.

140. D'Amico, R., et al., *Ultramicronized Palmitoylethanolamide in the Management of Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation.* Int J Mol Sci, 2021. **22**(21).

141. Wang, J.X. and J.L. Voss, *Brain networks for exploration decisions utilizing distinct modeled information types during contextual learning.* Neuron, 2014. **82**(5): p. 1171-82.

142. Peritore, A.F., et al., *Management of Acute Lung Injury: Palmitoylethanolamide as a New Approach.* Int J Mol Sci, 2021. **22**(11).

143. Hu, J., et al., *Micronized Palmitoylethanolamide Ameliorates Methionine- and Choline-Deficient Diet-Induced Nonalcoholic Steatohepatitis via Inhibiting Inflammation and Restoring Autophagy.* Front Pharmacol, 2021. **12**: p. 744483.

144. Loomba, R., S.L. Friedman, and G.I. Shulman, *Mechanisms and disease consequences of nonalcoholic fatty liver disease.* Cell, 2021. **184**(10): p. 2537-2564.

145. Albanese, M., et al., *Effects of Ultramicronized Palmitoylethanolamide (um-PEA) in COVID-19 Early Stages: A Case-Control Study.* Pharmaceuticals (Basel), 2022. **15**(2).