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Review

Therapeutic Use of Palmitoylethanolamide as an Anti-Inflammatory and Immunomodulator

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Abstract: Palmitoylethanolamine (PEA) is an endocannabinoid-like compound first encountered within the lipid fractions of specific foods and has intrigued researchers since the 1950s due to its therapeutic effects. This survey aims to explore the therapeutic promise held by PEA as an anti-inflammatory and immunomodulatory agent. The therapeutic impact of PEA reverberates across diverse physiological systems, such as the central nervous system, gastrointestinal tract, vascular network, and the digestive and respiratory system. Additionally, it is effective in pain management and reducing 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

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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 the enzymes involved in the biosynthesis and metabolism processes of these endocannabinoids [1].

The 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, 2-arachidonoylglycerol (2-AG) was described [3]. Despite the fact that anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the best-characterized endocannabinoids, other endogenous compounds, also named endocannabinoids, were recently discovered. As classical endocannabinoids, they are capable of binding to cannabinoid receptors: *N*-dihomo-γ-linolenoyl ethanolamine and *N*-oleoyl dopamine [1], 2-arachidonoylglycerol ether (noladin ether, 2-AGE) [4], O-arachidonoylethanolamine (virodhamine) [5], and *N*-arachidonoyldopamine (NADA) [6].

Endocannabinoids are synthesized alongside cannabinoid receptors in a state of inactivity, and they are composed of mono- or di-unsaturated compounds referred to as endocannabinoid analogs. These analogs have been documented for their ability to produce cannabimimetic effects [7]. Additionally, 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 oleoylethanolamine (OEA) [1], Stearoylethanolamide [7] and palmitoylethanolamine (PEA) [7].

Palmitoylethanolamide (PEA) is an endogenous compound initially identified through lipid fractions found in soy, egg yolk, and peanuts [8,9]. It is commonly found in food sources such as soybean sprouts, roasted coffee, black-eyed peas, apples, and potatoes [9], and also in human milk [10]. In animals, PEA synthesis occurs through the hydrolysis of its direct phospholipid precursor, *N*-palmitoyl-phosphatidylethanolamine, via the action of *N*-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) [11].

The pharmacological activities of PEA were first described in the mid-1950s, when [9] 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 [12]. Currently, there is evidence supporting its use as an immunomodulator [13], in analgesia [14], in managing hypersensitivity [14], and in altering the neurological activities of the central nervous system, such as in Alzheimer's disease [15] multiple sclerosis [16], and sciatic nerve injuries [17]. Furthermore, PEA has significant potential as an anti-inflammatory agent [18]. 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 [19]. The local autacoid anti-inflammatory antagonism hypothesis suggests that PEA can inhibit mast cell degranulation locally and reduces negative feedback during inflammation [20]. 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) [21]. It may also interact with G protein-coupled receptor 55 (GPR55), which has anti-anaphylactic effects by acting on mast cells [22]. Interestingly, PEA does not bind to cannabinoid receptors, but it can increase the concentration of anandamide (AEA), enhancing its action [19]. These various therapeutic targets highlight the potential of PEA as an anti-inflammatory and immunomodulatory tool [18]. 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 at the end of the 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 [23].

Pioneering studies conducted by researchers like Raphael Mechoulam [24] 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) [25,26], their endogenous ligands: classical endocannabinoids (e.g., anandamide or *N*-arachidonoylethanolamine and 2-arachidonoylglycerol) and endocannabinoid-like compounds (e.g., PEA, OEA, SEA) [7], and the metabolic enzymes responsible for synthesizing and degrading endocannabinoids [27]. 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) [28,29], as targets for cannabinoid ligands.

Matsuda et al., 1990, demonstrated the first cannabinoid receptor in rats, the cannabinoid receptor type 1 (CB1), primarily locating it in the brain [25]. Later on, the cannabinoid receptor type 2 (CB2) was identified through homology cloning, mainly found in the immune system [26,30]. 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 [27,31]. 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 [27].

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 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 [32].

In 1986, 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 [33]. Most of CB1 in the nervous system is located presynaptically, where it binds endocannabinoids released from the postsynaptic neuron (retrograde signaling); however, postsynaptic signaling and astrocyte expression have also been described [34].

In the retrograde mechanism, 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 Ca^{2+} influx via voltage-gated Ca^{2+} channels (VGCCs) [35]. 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 [36]. For example, 2-AG is produced in response to an increase in intracellular Ca^{2+} concentration and/or activation of Gq/11-coupled receptors [34,37]. 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 Ca^{2+} channels, thereby reducing presynaptic Ca^{2+} influx; secondly, by inhibiting adenylate cyclase (AC) and the subsequent cAMP/PKA pathway [34,37,38]. This ultimately leads to the degradation of 2-AG by monoacylglycerol lipase (MAGL) [34,37].

In postsynaptic signaling, endocannabinoids have the ability to influence neural function and synaptic transmission by interacting with both transient receptor potential TRPV1 (vanilloid receptor type 1) and CB1Rs situated on or inside the postsynaptic cell [34].

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 Ca^{2+} signaling. Glutamate released from astrocytes activates presynaptic mGluR1s to enhance its release and postsynaptic NMDARs to initiate a slow inward current [34].

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 [39].

Among the receptors targeted by endocannabinoids, TRPV1 has been extensively characterized and studied [28]. It is predominantly found in primary afferent nerve fibers [28]. The ion channels associated with transient receptor potential (TRP) receptors, like TRPV1, exhibit a structural arrangement comprising six transmembrane domains, with a pore region positioned between the fifth and sixth domains. Additionally, these channels feature lengthy intracellular N-terminal and C-terminal domains. The N-terminal tail contains six ankyrin repeat domains, facilitating interactions with calmodulin (CaM) and ATP [35]. Moreover, the C-terminal tail includes a TRP domain and sites for binding with calmodulin (CaM) and phosphoinositide 4,5-bisphosphate (PIP2) [35].

TRPV1 assumes a pivotal role in processes related to pain, nociception, and heat perception [40]. Its initial discovery took place in primary afferent nociceptors located in the dorsal root ganglia (DRGs), trigeminal ganglia, and vagal ganglia [41]. Subsequently, TRPV1 was identified in various regions of the central nervous system, including dopaminergic neurons within the substantia nigra, as well as the 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 [42,43].

TRPV1 is characterized by being activated by xenobiotics, including pungent compounds like capsaicin and piperine, high temperatures, and low extracellular pH. Additionally, it is worth noting that TRPV1 undergoes significant regulation and sensitization in the presence of inflammatory conditions. This heightened sensitivity to stimuli plays a role in both the initiation and perpetuation of intestinal inflammatory processes [42].

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that become activated when bound to specific ligands. They play a pivotal role in controlling the expression of genes that are essential for cellular differentiation and a wide range of metabolic processes [44]. 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 [44]. The PPAR family comprises three isoforms, α, δ (also known as β), and γ, whose binding recruits additional regulatory proteins involved in transactivation modulation [45].

PPARs play a fundamental role in inflammation [46], mediating the modulation of the inflammatory response through various mechanisms, such as the inhibition of pro-inflammatory factors (e.g., leukotrienes and interleukins) [47]. Accordingly, it is known that the duration of inflammation tends to be longer in mice deficient in PPARs [47].

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 [45]. 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 [48]. 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 [49]. The 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 [49].

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) [50]. In its active form, PPARα binds to DNA elements, increasing the transcription of various anti-inflammatory proteins, such as IκB-α [51].

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 [52]. GPR55 has been identified in various regions, including the brain, specifically in areas related to memory, learning, and motor functions, as well in the ileum, testicles, amygdala, breast, omental adipose tissue, and some endothelial cell lineages [53]. 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 [43,54].

Below is a summary table (Table 1) of non-cannabinoid binding targets of endocannabinoids.

Table 1. Main atypical 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; TRPV8: Transient Receptor Potential Vanilloid 8; PPARα: Peroxisome proliferator-activated receptor alpha; PPARγ: Peroxisome proliferator-activated receptor gamma. Table is adapted with permission from [1], Pertwee, 2015.

4. Palmitoylethanolamide (PEA): A Promising Therapeutic Lipid

In 1965, Bachur and colleagues identified the presence of PEA in the brains, livers, and skeletal muscles of rats [55]. 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 [56].

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 [9]. 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. 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 [1], 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) [11]. The degradation of PEA into palmitic acid and 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) [57]. 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 [57]. FAAH expression may be higher in the brain and liver, while NAAH is prevalent in the intestine and macrophages [56].

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 [11,58]. 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 [56]. Therefore, the oral absorption of PEA is quite complex, limited by the dissolution rate, showing an inverse relationship with particle size [59].

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 [60]. Torino et al., 2016 [61] 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 [62]. Another interesting study by Petrosino et al. (2018) demonstrated that ultra-micronized PEA was detectable in the bloodstream within 5 min of administration, with a peak plasma concentration of 5.4 $\pm$ 1.87 pmol/mL, whereas non-ultra-micronized PEA did not produce a significant peak plasma concentration [63]. 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 h [64]. They observed that PEA plasma concentrations doubled within 2 h and returned to baseline levels after 4 h.

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 the 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 [65,66].

PEA distribution was described in the study by Zhukov et al. (1999) after the intraperitoneal administration of radiolabeled PEA in rats [67]. 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 [68]. Additionally, regarding

the distribution of PEA in the body, Svobodova, et al., 2023 [69] 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 [70]. FAAH is an intracellular membrane-bound serine hydrolase, predominantly identified in mammalian tissues, with higher abundance in the brain and liver [71]. 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 [60]. To date, the only known information is related to its protective role in the kidney in hypertensive injury in rats, involving the reduced 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 [72].

4.2. Possible Pharmacological Targets and Mechanisms of Action

The 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 compound 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 [73]. PEA acts as a GPR55 agonist (EC values are 4, 19,800 and >30,000 nM at GPR55, CB and CB receptors, respectively) and directly activates PPARα (EC = 3 μM) [74]. 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 [60].

The first hypothesis about the action of PEA emerged from studies by Aloe et al. (1993) [20]. They conducted an animal model study with Sprague Dawley rats treated with long-chain and short-chain *N*-acylethanolamines during inflammation induced by the substance 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 PEA [75]. 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 PEA, and clinical improvement in the lesions was observed, suggesting that PEA could be an alternative to corticosteroid therapy for these skin conditions [76].

The concept of the entourage effect suggests that PEA enhances the antinociceptive (pain-relieving) and anti-inflammatory properties of other naturally occurring compounds by either boosting the receptors' attraction to them or by hindering the breakdown of these compounds through metabolic processes [23,77]. One of these endogenous compounds is AEA, whose activity can be potentiated by PEA to increase pharmacological effects, as demonstrated by Ho, Barrett and Randall (2008) in an experimental model with male Wistar rats studying the third-order branches of the superior mesenteric artery [78]. 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.

The effect of endogenous PEA can also be synergistically stimulated through the administration of exogenous compounds when given orally, as proposed by Del Re et al. (2022) [79]. 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 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)

The 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. (2001) conducted an in vitro study that examined PEA and AEA activities in intracellular Ca^{2+} binding assays, TRPV1 receptor binding assays, and AEA hydrolase activity assays [80]. These authors synthesized these compounds from arachidonic acid or palmitic acid and ethanolamine. They observed an increase in AEA-mediated TRPV1 action in $[Ca^{2+}]i$, suggesting an intensification of AEA actions mediated by TRPV1. PEA at a concentration of 5 μM (i.e., the same range as seen for its effects upon PPAR-α) potentiated the ability of AEA to activate TRPV1-mediated calcium influx by reducing its EC_{50} value from 0.44 to 0.22 μM. Ambrosino et al. (2013) reported similar results from an in vitro study using F11 and CHO cells in pain inducers like capsaicin or bradykinin. They observed a molecular mechanism for the action of PEA on TRPV1. They proposed that the activation of TRPV1 channels by ethanolamide triggers membrane depolarization, leading to a substantial increase in $[Ca^{2+}]i$. PEA elicits calcium transients (EC_{50} 3 μM) in a manner reduced (but not blocked) by the TRPV1 antagonists capsazepine and SB-366791 (the latter at a concentration that completely blocked the response to capsaicin) [81].

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 [64]. 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 [78]. In an experimental model of intestinal inflammation induced via the 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 [82]. 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 [59].

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 [83].

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 [84].

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 [85].

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 [83]. Combining PEA with tramadol also reduced sedation while enhancing its analgesic effect, further highlighting its potential synergistic actions involving TRPV1 and PPAR-α receptors [86].

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 [87].

Through the activation of 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 [88]. 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 [89].

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 [90].

Overall, the 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 [54]. The authors demonstrated the expression of the GPR55 receptor in mouse tissues, where receptor mRNA was found in the adrenal glands, gastrointestinal tract, and 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 a study conducted by Rinne et al. (2018) in adult male and female mice deficient in GPR55 treated with PEA at 3 mg/kg via intraperitoneal injection for 4 weeks [91]. 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 [91].

Marichal-Cancino et al. [92] demonstrated that the intravenous administration of PEA inhibits vasopressor responses to sympathetic stimulation and exogenous norepinephrine

and induces hypotension in Wistar rats, 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. [93] demonstrated that PEA can increase the aqueous humor outflow through the trabecular meshwork 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) [94]. The researchers showed that the 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 [94].

Another interesting study involving spinal cord injury was conducted by Crupi et al. (2016) with the intraperitoneal administration of the PEA with luteolin in an ultramicronized formulation (co-ultraPEALut) in mice. Co-ultraPEALut presented regenerative capacity and an immunomodulatory profile that 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) [95]. Co-ultraPEALut can also be used in cerebral ischemia, as proposed by Caltagirone et al. (2016) [96]. 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 [96]. 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 [96].

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 the 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) [21].

A sciatic nerve injury model was proposed by Gugliandolo et al. (2018) with the oral administration of PEA with oxazoline (PEA-OXA) to mice [17]. PEA-OXA is a modification of PEA, where an oxazoline ring structure is added to the molecule. This modification may alter its pharmacological properties and could potentially enhance its effects on the endocannabinoid system or other biological pathways [97]. PEA-OXA displayed anti-inflammatory and neuroprotective activity, reduced edema, mast cell infiltration, c-Fos and NAAA expression 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 [17]. 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 [98].

PEA-OXA performance and mechanism were also tested in a rat model of cerebral ischemia in diabetic rats that were 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) [99].

5.1.1. Neuroinflammation

Neuroinflammation is defined as an inflammatory reaction that impacts the brain or spinal cord. This response is orchestrated through the generation of cytokines, chemokines, reactive oxygen species, and secondary messengers, which are produced by glial cells like astrocytes, as well as by endothelial cells and immune cells that originate from outside the central nervous system [100]. 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 [101].

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 in controlling neuroinflammation. PEA displayed a neuroprotective role, attenuating Aβ-induced astrocyte activation and 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 [102,103]. D'Aloia et al. (2021) also proposed an in vitro neuroinflammation model using microglial cells (N9) induced by lipopolysaccharide (LPS). In this model, it 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 [104].

Furthermore, in an experimental rat model, the intraperitoneal administration of PEA had neuroprotective and anti-inflammatory effects [83]. The fatty acid derivative reduced TNF-α expression, p65 transcription factor, inducible nitric oxide synthase [83] 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 effects of PEA when added to the diet of obese mice in relation to anxiety-related neuroinflammation [105]. 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) [106]. 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.

Co-ultraPEALut, as evidenced by Paterniti et al. (2013) [107], when injected intraperitoneally into mice, 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 [108]. 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) [109]. 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 [110]. In vitro studies also demonstrated 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 Aβ 1-42 exposure, with these effects being correlated with the activation of PPAR-α receptors [111].

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 [15]. Additionally, it 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) [15]. 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 [112]. 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 [113]. The development of vascular dementia is correlated with obesity, insulin resistance, diabetes, hyperhomocysteinemia, hypertension, and hyperlipidemia, conditions that promote an inflammatory state in the body [113].

Impellizzeri et al. (2019) proposed the use of PEA-OXA in mice through oral administration, observing the neuroprotective effect of 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 [114]. Another effect of PEA-OXA administration was the ability to pre-

vent 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 [114].

5.1.4. Multiple Sclerosis and Amyotrophic Lateral Sclerosis

Multiple sclerosis is a non-traumatic disabling disease classified as an autoimmune disease and is common in adults and young individuals [115], exhibiting a heterogeneous symptomatology with distinct signs due to impairment of the motor, sensory, visual, and autonomic systems [116].

The inflammatory processes in multiple sclerosis are the main factor contributing to the development of lesions [115]. 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-ultraPEALut) 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 [16].

PEA was also used as therapy for a neurodegenerative disease, amyotrophic lateral sclerosis (ALS), characterized by the progressive loss of motor neurons, resulting in muscle atrophy, paralysis, and a typically short life expectancy of 3–5 years from symptom onset. In ALS, the inflammation of neurons is primarily driven by microglia and mast cells and there are no effective therapies for this condition. The outcomes of the PEA's treatment indicated notable improvements in the patient's clinical condition, as evidenced by electromyographic analysis and pulmonary function. The text suggests that palmitoylethanolamide's effectiveness in this context may be attributed, at least in part, to its ability to reduce the activation of mast cells and microglia [117].

5.1.5. Acute Mania

In a recent clinical trial conducted by Abedini et al. in 2022, the efficacy and safety of a combined therapy involving PEA in the treatment of acute mania were thoroughly investigated. This randomized, double-blind, and placebo-controlled study focused on patients in the acute phase of mania and divided them into two parallel groups. One group received a combination of lithium (maintaining a blood level of 0.8–1.1 mEq/L) and risperidone at a dosage of 3 mg, along with palmitoylethanolamide at 600 mg, administered twice daily for a duration of 6 weeks. The second group received a placebo under the same regimen. Throughout the study, all participants were meticulously assessed using the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), and Extrapyramidal Symptom Rating Scale (ESRS). The results of the trial were compelling, with the PEA combination therapy demonstrating a significant reduction in YMRS scores, indicating an improvement in manic symptoms. This study affirms that PEA, when used as an adjunctive medication, effectively enhances the management of manic symptoms and contributes to an improved overall clinical status during acute episodes of mania [118].

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. The Table 2 presented in vivo experimental studies, the Table 3 presented in vitro experimental studies and the Table 4 presented clinical studies.

Table 2. Main effects of Palmitoylethanolamide in experimental models of nervous system pathologies.

	Pathological Condition	Experimental Model	Strain	Sex	Age	Formulation	A.R.	Main Effect	Receptor	Reference
Nervous System	AD	Mice	3 × Tg-AD	M	9 m	PEA-um	s.c.	Neuroprotective and anti-inflammatory	-	[109]
	AD	Mice	SAMP8	-	4 m	PEA	p.o.	Anti-inflammatory	-	[15]
	Multiple Sclerosis	Mice	C57BL/6	-	-	co-ultraPEALut	i.p.	Anti-inflammatory and immunomodulator	-	[16]
	Anxiety associated with neuroinflammation	Mice	C57Bl/6J	M	6 w	PEA	p.o.	Anti-inflammatory	PPAR-α	[105]
	Neuroinflammation	Mice	C57BL/6J	M	10–12 w	PEA	i.p.	Anti-inflammatory	PPAR-α	[106]
	Neuroinflammation	Mice	CD1	-	-	co-ultraPEALut	i.p.	Anti-inflammatory	PPARα and PPARβ	[107]
	Experimental spinal cord injury	Mice	CD1	M	Adult	PEA	i.p.	Anti-inflammatory and immunomodulator	PPARα	[94]
	Vascular dementia	Mice	CD1	M	-	PEA-OXA	p.o.	Neuroprotective	-	[114]
	Spinal Cord Injury	Mice	CD1	M	-	co-ultraPEALut	i.p.	Regenerative and immunomodulator	-	[95]
	Cerebral ischemia	Rat	Wistar	M	-	Co-ultraPEALut	i.v.	Anti-inflammatory and immunomodulator	-	[96]
	Focal cerebral ischemia	Rat	Wistar	M	-	PEA-OXA	i.v.	Anti-inflammatory and immunomodulator	-	[99]
	Spinal Cord Injury	Mice	CD1	-	-	PEA	i.p.	Neuroprotective and anti-inflammatory	PPAR-δ PPAR-γ	[21]
	Sciatic nerve injury	Mice	CD1	M	-	PEA-OXA	p.o.	Neuroprotective and anti-inflammatory	-	[17]
	Sciatic nerve injury	Mice	Mutants	-	-	PEA	s.c.	Neuroprotective and anti-inflammatory	PPAR-α	[98]

AD: Alzheimer's disease; M: male; w: weeks; m: months; PEA-um: micronized Palmitoylethanolamide; co-ultraPEALut: Ultramicronized Palmitoylethanolamide with Luteolin; PEA-OXA: Palmitoylethanolamine with oxametazoline; A.R.: administration routes; s.c.: subcutaneous; p.o.: oral; 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-ultraPEALut	Aβ 1-42toxicity	Anti-inflammatory	PPAR-α	[111]
	Neuroinflammation	In vitro	PEA	N9 microglial cells	Neuroprotective	CB_2	[104]
	Neuroinflammation	In vitro	PEA	Microglial astrocyte co-cultures	Neuroprotective	PPAR-α	[102]
	Neuroinflammation/ Neurodegeneration	In vitro	PEA	Astrocyte culture	Anti-inflammatory	PPAR-α	[103]

AD: Alzheimer's Disease; co-ultraPEALut: Ultramicronized Palmitoylethanolamide with Luteolin.

Table 4. Effect of Palmitoylethanolamide in patients with nervous system disorders.

	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-ultraPEALut (S.L.)	700 mg + 70 mg	2 m	Clinical improvement	[96]
Nervous System	ALS	Case report	-	-	ultra-PEA	-	-	Clinical improvement	[117]
Central Nervous System	Acute Mania	randomized, double-blind, and placebo-controlled study	Men and women		PEA association	600 mg	1.5 m	improvement in manic symptoms	[118]

S.L.: sublingual route; m: months; co-ultraPEALut: Ultramicronized Palmitoylethanolamide with Luteolin, ultra-PEA: ultramicronized Palmitoylethanolamide.

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, and lowered levels of nitrite/nitrate (NO^{2-}/NO^{3-}) and malondialdehyde [119]. LoVerme et al. (2006) also showed a reduction in hyperalgesic responses due to the anti-inflammatory effect of PEA, when 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 [120]. 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 [121].

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 PGE_2. The lipid exerted a local peripheral antinociceptive effect, which the authors attributed to the activation of ATP-sensitive K(+) channels [122]. 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 [123]. Additionally, in 2013, the same group 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 [14]. 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 the endogenous activation of the endocannabinoid system following intense exercise [124]. 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 PEA (PEA-um). After rat paw injury, there was relief in mechanical allodynia, thermal hyperalgesia, and motor coordination. Pre- and post-injury treatments 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 [125].

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 pronociceptive 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 [63]. In the same model of rat paw edema, induced by carrageenan, PEA administration via intracerebroventricular, reduced inflammation and hyperalgesia by interaction with PPAR-α [126].

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 cells, and mechanical pain threshold, along with a significant reduction in the expression of c-Fos protein, NGF, TNF-α, and IL-1β [127]. The analgesic effect of PEA was correlated with its anti-inflammatory capacity, as observed by De Filippis et al. (2011) [128]. 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 [129]. PEA-um was administered orally to alleviate 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 in IL-1β, COX-2 expression, and iNOS [129]. 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 [130].

In the same context, the synergic action of PEA-OXA was investigated by Petrosino et al. (2017) in the neuropathic and inflammatory pain model. Through oral administration to rats and mice, PEA-OXA demonstrates 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 [131]. 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 [131].

The therapeutic potencial of PEA to treat inflammatory conditions, alleviate pain and modulate the immune system tested in experimental models were summarized in Table 5.

Gatti et al., 2012 evaluated the effectiveness and safety of PEA in alleviating pain severity among patients suffering from various pathological conditions. PEA was administered at a dose of 600 mg twice daily for three weeks, followed by a once-daily dose for four weeks for 610 patients. The primary outcome measure was the assessment of pain severity using the numeric rating scale. PEA treatment led to a significant reduction in mean pain severity scores in all patients who completed the study. Remarkably, the effectiveness of PEA was consistent across various pathological conditions contributing to pain. Importantly, no adverse effects or safety concerns were associated with PEA use [132], as shown in Table 6

In a randomized, placebo-controlled, double-blinded crossover trial, 14 healthy volunteers took either PEA (3 × 400 mg per day) or a placebo over a 4-week period. They examined PEA's mode of action using a well-established pain model known as "Repetitive phasic heat application", which is adept at assessing analgesic and anti-hyperalgesic effects in healthy individuals. Peripheral and central sensitization, as well as pain modulation, were evaluated. PEA treatment led to a significant reduction in repetitive heat pain, an extension of cold pain tolerance, an increase in pressure pain tolerance, and improved conditioned pain modulation. Furthermore, PEA treatment resulted in a reduction in the wind-up ratio and the average distance of allodynia while also increasing heat pain tolerance. In summary, PEA's analgesic properties act on both peripheral and central pain mechanisms, as well as pain modulation [133], as shown in Table 6.

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 the joints in the knees, hands, hips, and spine [134]. The primary treatment involves the use of analgesics; however, continuous use can result in adverse reactions such as gastric ulcers and bleeding [135].

A recent study from 2021 conducted by researchers in South Korea [136] 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, and alleviated inflammation, as evidenced by a reduction in the mRNA expression of iNOS, 5-Lox, COX-2, TNF-α, and IL-1β. Moreover, it modulated the expression of matrix metalloproteinases and tissue inhibitors 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 [137]. 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, Table 5.

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 in 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 [13], as shown in Table 5.

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

	Pathological Condition	Experimental Model	Strain	Formulation	A.R.	Main Effect	Receptor	Reference
Pain and inflammatory processes	Post-operative pain	Rat	Sprague Dawley	PEA-um	p.o.	Anti-inflammatory and analgesic	-	[125]
	Sciatic nerve injury	Rat	Sprague Dawley	PEAum-Paracetamol	p.o.	Anti-inflammatory and analgesic	-	[127]
	Sciatic nerve injury	Mice and Rat	Swiss and Sprague Dawley	PEA	i.pl.	Anti-inflammatory and analgesic	PPAR-α	[120]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	K+ channel	[122]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	nNOS	[123]
	Hyperalgesia	Rat	Wistar	PEA	i.pl.	Antinociception	CB_2	[14]
	Paw edema	Rat	Sprague Dawley	PEA-um	p.o.	Anti-hyperalgesic and anti-inflammatory	-	[63]
	Paw edema	Rat	Sprague Dawley	PEA-um and LAC	p.o.	Anti-inflammatory and analgesic	-	[129]
	Paw edema	Mice	Swiss	PEA	i.c.v.	Anti-hyperalgesic and anti-inflammatory	PPAR-α	[126]
	Inflammatory and neuropathic pain	Rat	Sprague Dawley	PEA	i.p.	Anti-hyperalgesic and anti-inflammatory	-	[130]
	Inflammatory and neuropathic pain	Mice and Rat	Sprague Dawley and mutant mice	PEA-OXA	p.o.	Anti-inflammatory and immunomodulatory	PPAR-α.	[131]
	Acute inflammation	Rat	Wistar	PEA	p.o.	Anti-inflammatory	-	[119]
	Osteoarthritis	Rat	Sprague Dawley	PEA	p.o.	Anti-inflammatory and immunomodulatory	-	[136]
	Osteoarthritis	Mice	DBA	co-ultraPEALut	i.p.	Anti-inflammatory	-	[137]
	Hypersensitivity	Mice	BALB/c	PEA	p.o.	Immunomodulatory	-	[13]
	Chronic granulomatous inflammation	Rat	Wistar	PEA	s.c.	Anti-inflammatory and immunomodulatory	-	[128]

PEA-um: Micronized Palmitoylethanolamide; co-ultraPEALut: Ultramicronized Palmitoylethanolamide with Luteolin; PEA LAC: Palmitoylethanolamide Acetyl-L-carnitine; 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.

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 PEA through intravenous administration in rats, observing its anti-inflammatory and neuroprotective activity [138]. They found that PEA increased platelet count and fibrin concentration while prothrombin time, 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 [138], as shown in Table 7.

Mattace et al., 2013, showed a protective role of PEA in the kidneys of spontaneously hypertensive rats (SHR). The protection of hypertensive injury in rats involved reducing the expression of the enzyme epoxygenase CYP2C23 and soluble epoxide hydrolase. This reduction was 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, [72] as shown in Table 7.

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 [139].

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 of CB2, GPR55, and PPARα receptors [59].

Another similar study involving colitis was conducted by Peritore et al., 2021, but the authors used the compound PEA/Pol-co, which combines PEA with polydatin, a derivative of fatty acid [140]. 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 [140].

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) [141]. 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) [142]. 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 [143].

Hu et al. (2021) observed that PEA significantly attenuated the progression of non-alcoholic steatohepatitis, relieved oxidative stress, reduced gene expression related to lipid 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 [142], as shown in Table 7.

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), as shown in Table 7. 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 [140]. 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 [140].

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 [144], as shown in Table 6.

5.6. Therapeutic Potential of PEA in Glaucoma

Costagliola et al., 2014, evaluated the effects of administering PEA orally to patients with normal-tension glaucoma (NTG). NTG is a form of glaucoma where patients experience damage to the optic nerve and vision loss even though their intraocular pressure (IOP) is within the normal range. The study enrolled 32 consecutive NTG patients and randomly divided them into a treated group or no treated group. The PEA-treated group received 300 mg ultramicronized-PEA tablets twice a day for six months. After six months, the PEA-treated group experienced a reduction in IOP, dropping from an average of 14.4 mm Hg to 11.1 mm Hg. Notably, visual field parameters, which are indicative of the progression of glaucomatous damage, decreased significantly in patients receiving PEA, while no such changes were seen in the untreated group. This research suggests that PEA may hold promise as a potential treatment option for NTG by helping to manage IOP and slowing the progression of glaucomatous visual field damage [145], as shown in Table 6.

5.7. Therapeutic Potential of PEA in Dermatological Conditions

A monocentric, randomized, double-blind, and comparative trial involving 60 patients with asteatotic eczema, graduated as mild to moderate skin dryness, was conducted to test PEA and AEA as a topic emollient. The treatment with PEA and AEA was compared to emollients, commonly containing ingredients like urea, lactic acid, or lactate salts. Over a 28-day period, the subjects' skin barrier function and sensory perception threshold were assessed using both clinical scoring and bioengineering technology. While improvements were observed in both emollient groups, the one containing PEA and AEA demonstrated superior changes in skin surface capacitance. Notably, the most remarkable outcome was the PEA/AEA emollient's ability to restore the 5 Hz current perception threshold to a normal level within just 7 days, with a significant difference observed between the baseline and day 14 values. In the PEA/AEA emollient group, the 5 Hz current perception threshold displayed a positive and significant correlation with skin surface hydration and a negative correlation with transepidermal water loss. This suggests that the PEA/AEA emollient has a notable impact on sensory perception and skin barrier function, making it a promising option for the management of AE [146], as shown in Table 6.

Table 6. Effect of PEA treatment in humans disorders.

	Pathological Condition	Clinical Trial	Sex	Age	Formulation	A.R.	Dosage	Time	Main Effect	Reference
Respiratory system	COVID-19	Case-control	Men and women	18–80 years old	PEA-um	p.o.	1800 mg	28 d	Anti-inflammatory and immunomodulator	[144]
Optic nerve	NTG	Randomized	Men and women	-	ultra-PEA	p.o.	300 mg	6 m	Decreased glaucoma damage	[145]
Neurvous system	Allodinya	randomized, placebo-controlled, double-blinded crossover trial	Men and women	-	PEA	p.o	1200 mg	1 m	Reduction of Allodinya	[133]

Table 6. *Cont.*

	Pathological Condition	Clinical Trial	Sex	Age	Formulation	A.R.	Dosage	Time	Main Effect	Reference
Skin	asteatotic eczema	monocentric, randomized, double-blind, and comparative trial	Men and women	-	PEA-AEA	topical	-	1 m	Reduction of the injury	[146]
Neurvous system	Chronic Pain	observational study	Men and women	-	PEA	p.o.	1200 mg	2 m	Reduction of chronic pain	[132]

PEA-um: Micronized Palmitoylethanolamide; A.R.: administration routes; p.o.: Oral; ultra-PEA: Ultra-Micronized Palmitoylethanolamide; d: days; m: months.

Table 7. 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	Strain	Formulation	A.R.	Main Effect	Receptor	Reference
Gastrointestinal System	Intestinal inflammation	Rat	Mutants	PEA	i.v.	Anti-inflammatory and immunomodulator	-	[139]
	Colitis	Mice	ICR	PEA	p.o.	Anti-inflammatory	TRPV1 and CB_1	[59]
	Colitis	Mice	CD1	PEA-um + Paracetamol	p.o.	Anti-inflammatory	-	[140]
	Inflammatory bowel disease	Zebrafish Larvae	Wild (WT)	PEA-OXA	-	Anti-inflammatory	-	[141]
Vascular System	Coagulopathy	Rat	Sprague Dawley	PEA-um	p.o.	Anti-inflammatory and neuroprotective	-	[138]
Vascular System	Hypertension	Rat	SRH	PEA	s.c.	Anti-inflammatory and antioxidant	-	[72]
Digestive system	Steatohepatitis	Mice	C57BL/6	PEA	p.o.	Anti-inflammatory	PPAR-α	[142]
Respiratory system	Acute lung injury	Mice	CD1	PEA-um	p.o.	Anti-inflammatory and immunomodulator	-	[140]

PEA-um: Micronized Palmitoylethanolamide; PEA-OXA: Palmitoylethanolamine with oxazoline; A.R.: administration routes; p.o.: oral; i.v.: intravenous; s.c.: subcutaneously.

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. 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, and 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.

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