Pain Relief SAP

*Science-based micronized palmitoylethanolamide for pain management**

Pain, especially chronic pain affects a huge proportion of the population worldwide and results in serious impairment of quality of life.* Pain management is challenging, and several pharmacological treatment approaches exist, however, these therapeutic options do not provide complete pain relief, and result in significant side effects.* Palmitoylethanolamide (PEA) is a member of the endocannabinoid fatty acid amides and exhibits potent anti-inflammatory and analgesic properties.* Extensive clinical evidence supports the pleiotropic effects of PEA, where it appears to exert it's therapeutic effects via more than one mode of action, by modulating the endocannabinoid system in a safer and therapeutically efficacious manner.*

MICRONIZED PEA FOR ENHANCED BIOAVAILABILITY

PEA is poorly water-soluble affecting oral absorption and bioavailability.* Micronization helps reduce large PEA particles to the micron range (<10 µm), providing a larger total surface area and enables rapid dissolution and therapeutic efficacy corroborated by preclinical evidence.* **Pain Relief SAP** provides high quality micronized PEA for enhanced absorption, bioavailability and efficacy.*

Pain Relief SAP can mitigate painful diabetic neuropathy, alleviate lumbosciatic pain and pain due to carpal tunnel syndrome, joint arthritis and pelvic pain associated with endometriosis and primary dysmenorrhea.* **Pain Relief SAP** can be a useful adjunct in chemotherapy, treatment of depression, management of migraine and irritable bowel syndrome.*

SUPPLEMENT FACTS

Serving Size: 2 Capsules
Servings Per Container: 60 or 30

	Amount Per Serving	% Daily Value
Palmitoylethanolamide (micronized)	600 mg	**
Devil's claw (*Harpagophytum procumbens*) extract, 5% harpagosides	60 mg	**

**Daily Value not established

Other ingredients: Microcrystalline cellulose, hypromellose, vegetable magnesium stearate, purified water, and silicon dioxide.

Contains no: Gluten, soy, wheat, eggs, dairy, yeast, citrus, preservatives, artificial colors and flavors, starch or sugar.

This product is non-GMO and vegan friendly.

Pain Relief SAP contains 120 capsules per bottle.

DIRECTIONS FOR USE

Adults: Take 2-4 capsules daily or as directed by your healthcare practitioner.
May take up to two weeks to notice the beneficial effects. Take daily for a minimum of two weeks for chronic pain relief. Consult a healthcare practitioner for use beyond 4 months.

INDICATIONS

Pain Relief SAP may help ameliorate migraine and symptoms of irritable bowel syndrome,* and can:

- Help manage painful diabetic neuropathy.*
- Be used to alleviate lumbosciatic pain and pain due to carpal tunnel syndrome and temporomandibular joint arthritis.*
- Help manage osteoarthritis and chronic pain.*
- Help mitigate pelvic pain associated with endometriosis and primary dysmenorrhea.*
- Be useful as an adjunct in chemotherapy providing analgesia and neuroprotection.*
- Be used as an adjunct in the management of major depressive disorder.*

CAUTIONS AND WARNINGS

Consult a healthcare practitioner prior to use if you are taking blood thinners.
Do not use if seal is broken. Keep out of reach of children.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for each **Pain Relief SAP** lot number have been tested by an ISO 17025 accredited third-party laboratory for identity, potency, and purity.

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

NFH®
351, Rue Joseph-Carrier, Vaudreuil-Dorion, Quebec, J7V 5V5
T 1 866 510 3123 • F 1 866 510 3130 • nfh.ca

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Pain, especially chronic pain affects a huge proportion (>40%) of the population worldwide, resulting in massive health and economic burden for individuals and society.[1] Debilitating conditions causing serious impairment of quality of life are characterized by presence of various kinds of pain such as low back pain, headache, dental pain and neuropathic pain.[1] Ailments such as osteoarthritis or rheumatoid arthritis result in tissue injury driving chronic inflammatory pain. Lesion or disease affecting the somatosensory system causes neuropathic pain.[2] Interestingly, pain related to chronic inflammatory/autoimmune conditions also manifest a neuropathic connection.[1, 2]

Treatment and management of pain are challenging, and several pharmacological treatment approaches exist that constitute a wide range of drug classes including anticonvulsants, antidepressants, opioids, acetyl-para-aminophenol (APAP), non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics.[1] However, these therapeutic options do not provide complete pain relief, and result in significant side effects. Elderly persons taking NSAIDs should be routinely monitored for potential gastrointestinal and hepatic risks, cardiovascular and renal side effects, and drug interactions. Tricyclic antidepressants and antiepileptic drugs have very poor tolerability and side effects, whereas opioid use presents challenges as they do not specifically act only on neurons, but also on non-neuronal cells such as microglia, astrocytes, and mast cells, triggering their activation and promoting further neuroinflammation.[3, 4] Noteworthy, major side effects resulting from these drugs are clearly attributable to the activation of non-neuronal cells.[1]

PALMITOYLETHANOLAMIDE

Palmitoylethanolamide (PEA) is a member of the N-acylethanolamine (NAE) family of fatty acid amides (endocannabinoids) and is structurally related to anandamide (AEA), another naturally occurring NAE. PEA is more abundant than AEA in many tissues and shares many pharmacological traits with endocannabinoids, including anti-inflammatory and analgesic properties.[1, 5] PEA is thought to constitute a "parallel" endocannabinoid signaling system, given the evidence that PEA production and inactivation can occur independently from that of AEA and 2-Arachidonoylglycerol.[5]

PHARMACOKINETICS AND MECHANISM OF ACTION

Different mechanisms of action have been proposed for PEA. PEA has been suggested to modulate and interact with mast cells, CB2-like cannabinoid receptors, ATP-sensitive K+-channels, TRP channels, and NFkB, however, the most prominent mechanism with substantial evidence is for the action of PEA upon the nuclear receptor peroxisome proliferator-activated receptor α (PPARα).[5] PEA is also shown to interact as an agonist with GPR119, an orphan receptor involved in glucagon-like peptide-1 secretion. These findings attest to the pleiotropic effects of PEA, where it appears to function as an anti-inflammatory and analgesic agent with more than one "mode of action," by modulating the endocannabinoid system in a safer and therapeutically efficacious manner.[6] It is important to note that PEA has been suggested to exert both receptor and non-receptor mediated effects at different cellular and tissue sites, indicating that this key pleiotropic trait makes it adaptable for the complexity of chronic pain.[5, 7]

MICRONIZATION FOR ENHANCED BIOAVAILABILITY

PEA is poorly water-soluble which affects the dissolution rate for oral absorption and bioavailability. Particle size is a critical aspect that influences dissolution rate.[5] Micronization helps reduce large PEA particles down to the micron range (<10 µm) and hence a larger total surface area, which allows the gastrointestinal milieu more access to free surfaces on the PEA particles and enables rapid dissolution.[1, 5] A preclinical study in inflammatory pain model has shown that orally administered micronized PEA is more efficacious than unmicronized PEA.[8]

CLINICAL INDICATIONS

Substantial evidence supports the use of PEA in a variety of pain treatment regimen, especially proving useful for pain treatment-resistant patients. A case series study demonstrated the efficacy of 600 mg/day dosage of PEA in seven different clinical cases such as metastatic prostate cancer, failed back surgery syndrome, severe chronic pain with dysesthesia, burning and hyperalgesia, chronic neuropathic pain, chronic idiopathic axonal polyneuropathy, low-back pain and paresthesia, as well as numbness.[9] The case series showed that a combination of PEA with regular analgesics did not lead to drug–drug interactions with excellent tolerability.[9]
The various clinical applications of PEA and their supporting clinical evidence are presented below:

DIABETIC NEUROPATHIC PAIN

PEA can be very useful in the management of painful symptoms experienced by diabetic patients with peripheral neuropathy. In one study, 600 mg of micronized PEA was supplemented to 30 diabetic patients suffering from painful diabetic neuropathy and pain symptoms were monitored before treatment start, after 30 and 60 days.[10] PEA supplementation showed a highly significant reduction in pain severity (evaluated by Michigan Neuropathy Screening instrument, Total Symptom Score, and Neuropathic Pain Symptoms Inventory). No adverse changes were found in the hematological and urine analyses associated with PEA treatment, and no serious adverse events were reported.[10]

LUMBOSCIATICA AND CARPAL TUNNEL SYNDROME

In a clinical study to evaluate the efficacy of PEA in the treatment of neuropathic pain due to lumbosciatica, 118 patients with neuropathic pain were assigned to standard treatment plus PEA (600 mg/day) or standard treatment for 30 days. PEA group showed significant improvement in pain relief.[11] In a review, researchers assessed 8 clinical trials comprising 1366 patients evaluating PEA's efficacy and safety in nerve compression syndromes: sciatic pain and pain due to carpal tunnel syndrome. PEA proved to be effective and safe in nerve compression syndromes. The authors highlighted a double blind, placebo-controlled trial in 636 sciatic pain patients, where, the number needed to treat to reach 50% pain reduction compared to baseline was 1.5 after 3 weeks of treatment.[12]

TEMPOROMANDIBULAR JOINT ARTHRITIS

PEA was evaluated at a dosage of 900 mg/day in a triple blinded randomized controlled clinical study comparing it's efficacy to ibuprofen in 24 patients with temporomandibular joint arthritis (TMJ) arthritis over a 2-week period. [13] PEA was found to significantly reduce pain compared to ibuprofen. Patients treated with PEA did not report any adverse events, whereas three patients in the ibuprofen group reported stomach-ache.[13]

ADJUNCT IN CHEMOTHERAPY

The adjunctive use of PEA in chemotherapy has been explored in a number of studies. In one study, PEA was added to a 2 month cytostatic regimen of patients suffering from Morbus Kahler, multiple myeloma, undergoing a treatment protocol consisting of bortezomib (1.3 mg/m^2 twice a week) and thalidomide (50-200 mg daily), presenting clear signs and symptoms of neuropathy and neuropathic pain. A significant reduction in pain and improvement in multiple neurophysiological measures were observed.[14, 15] The changes in neurophysiological measures suggest a positive action on myelinated fibre groups by PEA. It is also proposed that PEA potentially modulates mast cell hyperactivity and relieved conduction blocks secondary to endoneural edema.[14, 15]

Preclinical studies in leukemic animal models have shown that PEA may not only reduce polyneuropathic damage during and after chemotherapy, it may also enable oncologists to dose higher or longer in critical situations and enhance the efficacy and safety of chemotherapy.[14] Additionally, research evidence from cancer models supports cytostatic properties of PEA. PEA and related signaling lipids have been gaining attention as playing key roles in suppressing cancer growth.[14, 16, 17]

MIGRAINE

The characteristic features of migraine: pain, persistence and throbbing are mediated by increased sensitivity and the resultant activation of sensory neurons innervating intracranial meninges and their related large blood vessels. [18] In an open-label study attempting to assess the treatment efficacy of ultra-micronized PEA, fifty patients, suffering from migraine without aura, for at least 6 months with a frequency of monthly crises from 3 to 8 and with presence of headache from 4 to 12 days per month, were treated sublingually with 600 mg of PEA twice daily for 3 months.[18] Researchers observed that the mean number of days per month with migraine significantly decreased including pain intensity and a reduction of the number of analgesics taken. No serious adverse events were noted. However, more clinical trials are warranted to confirm the beneficial effects of PEA in migraine prevention.[18]

MAST CELL MODULATION

Mast cells (MCs) are immune-competent cells derived from bone marrow progenitors and act as signaling monitors against different types of injury by getting activated and regulating both innate and adaptive immune reactions. [19] MCs also perform crucial physiological roles regulating tissue remodeling, wound healing and neuroimmune response to stress.[19] MC granules contain several biological mediators that are released following activation by both immunoglobulin (Ig)E dependent and non-IgE-related stimuli leading to a more controlled mediator secretion. [19] The role of MCs in angiogenesis and hyperalgesia by modulating both acute allergic reaction and chronic inflammatory processes is well known.[19]

Growing evidence from preclinical studies suggests that PEA profoundly suppresses the activation of MCs. Such beneficial effect and the safety profile of PEA in regulating MCs have provided stimulus for researchers to evaluate PEA in clinical trials in various human diseases, especially in those conditions where MC activation is believed to be a primary cause of pathology.[19]

PELVIC PAIN ASSOCIATED WITH ENDOMETRIOSIS AND PRIMARY DYSMENORRHEA

Endometriosis is a common disorder characterized by chronic pelvic pain and pain during voiding, sexual intercourse, menstruation and defecation, due to triggering of mechanisms of hyperalgesia and allodynia of the pelvic visceral receptors generated by chronic inflammatory processes.[20] These processes are thought to be activated by estrogen and inflammation. Particularly, degranulating mast cells have been observed in higher quantities in endometriotic lesions than in unaffected tissues. In a small pilot study, four patients presenting endometriosis-related pain were enrolled and were administered 400 mg of PEA and polydatin 40 mg, twice daily for 90 days.[20] All patients experienced pain relief as early as 1 month after starting treatment in addition to improvements in endometriotic lesions (demonstrated by imaging) and reduction in analgesic drugs.[20] These findings have paved way for a multicenter pilot study to verify the effectiveness of this treatment in controlling chronic pelvic pain associated with endometriosis.[20]

Dysmenorrhea is the most common gynecologic disorder, and is highly prevalent during adolescence. In a clinical study with 220 young women aged 16 to 24 years who had primary dysmenorrhea, 110 patients were treated with the oral combination of PEA-transpolydatin: 400 mg + 40 mg (1 tablet a day for 10 days from the 24th day of cycle) and 110 patients with placebo.[21] Significant improvement of pelvic pain in the PEA and transpolydatin group compared to the placebo highlighting the efficacy of PEA as an adjuvant therapy in the medical treatment of primary dysmenorrhea in adolescents and young women.[21]

ADJUNCTIVE THERAPY IN MAJOR DEPRESSIVE DISORDER

It has been well recognized that PEA targets not only the peroxisome PPAR-α, but also the endocannabinoid system, binding the G-protein-coupled receptor 55, a non-CB1/CB2 cannabinoid receptor, and also the CB1/CB2 receptors, however with a weak affinity.[22] The efficacy of PEA as an adjunctive therapy was studied in patients with major depressive disorder (MDD). In this randomized double-blind, and placebo-controlled study, 58 patients with MDD and Hamilton Depression Rating Scale (HAM-D) score ≥ 19 were randomized to receive either 600 mg twice daily PEA or placebo in addition to citalopram for six weeks.[23] Patients in the PEA group exhibited significantly greater reduction in HAM-D scores compared to the placebo group starting from week 2 and the effects were sustained in the PEA group with greater improvement in depressive symptoms compared to the placebo group throughout the study period with no difference in side effects between both the groups.[23] These findings support the antidepressant and adjunctive therapeutic use of PEA in patients with major depressive disorder.[23] Nevertheless, more future studies in depressed patients are needed to confirm the mood-modulating properties of PEA.

INFLUENZA AND COMMON COLD

A systematic review surmised the role of PEA as an anti-inflammatory agent and as a therapeutic agent for influenza and common cold specifically focusing on 6 clinical trials in a total of nearly 4000 patients where PEA's effectiveness and safety for the treatment in these indications was shown.[24] Infections with virulent influenza viruses together with an aberrant and excessive inflammatory cytokine production. PEA is known for its anti-inflammatory activity due to it's inhibitory action on TNFα secretion in addition to the effect of PEA in modulating interleukins. These therapeutic properties of PEA attest to the observations of decreased influenza and common cold symptomatology in individuals treated with PEA.[24]

IRRITABLE BOWEL SYNDROME

A pilot randomised, double-blind, placebo-controlled, multicentre study explored the effects of PEA/polydatin 200 mg/20 mg or placebo twice daily on low-grade immune activation, endocannabinoid system and symptoms in 54 IBS patients.[25] Compared with placebo, PEA/polydatin profoundly decreased abdominal pain severity. Although more studies are required to elucidate the mechanism of action of PEA in IBS, these findings present a promising natural approach for pain relief.[25]

ALZHEIMERS DISEASE

Substantial preclinical evidence supports that PEA, especially in micronized or ultramicronized forms could be a valuable therapeutic option for treatment of different pathologies characterized by neurodegeneration, (neuro)inflammation, and pain. Noteworthy, neuroprotective effects of PEA have been demonstrated in multiple experimental models of Alzheimer's disease.[26] These warrant further investigation of PEA in Alzheimer's in large controlled clinical trials.

DEVIL'S CLAW EXTRACT

Devil's Claw (*Harpagophytum procumbens*) is a traditional South African herbal remedy used for rheumatic conditions and has been studied in the treatment for Osteoarthritis. The bioactive harpagoside in devil's claw has been associated for it's analgesic properties. Devil's claw extract has been associated with lower adverse effects compared to NSAIDs, and hence has garnered attention as a candidate in safe and efficacious pain management.[27]

SAFETY AND TOLERABILITY

PEA as described in multiple clinical studies has an excellent safety profile with minimal adverse events reported. [1, 2, 5] Further, PEA has been recognized to not induce pharmacological tolerance and does not interfere with poly-drug therapies.[1, 5]

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