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CONTENTS

Nutraceutical supplements for managing pain and inflammation: A special focus on palmitoylethanolamide and astaxanthin

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ABSTRACT: Several pharmacological agents have been employed to manage different pathological pain conditions, including NSAIDs, opiates, and others. However, adverse effects could restrict dosing and therapeutic effectiveness. In this review, we discuss nutraceuticals and various bioactive compounds, such as vitamins, carotenoids like lycopene and beta-carotene, and specific compounds like astaxanthin and palmitoylethanolamide (PEA), focusing on their roles in managing oxidative stress, inflammation, and pain. Palmitoylethanolamide (PEA), an endocannabinoid-like compound, is notable for its analgesic, anti-inflammatory, and neuroprotective actions, making it a promising therapeutic agent. The efficacy of PEA, especially in combination with natural antioxidants like astaxanthin, offers potential benefits for improved pain relief in conditions such as osteoarthritis. Micro-PEA, with improved pharmacokinetics and bioavailability, is effectively used to manage conditions like atopic dermatitis and chronic pain. Based on available literature, PEA is currently considered among the novel nonopioid interventions for chronic pain.

Key words: Astaxanthin, chronic pain, inflammation, nutraceutical, palmitoylethanolamide PEA

Chronic pain is increasingly being recognized and addressed in both humans and animals. Pain can be classified as transient, inflammatory, or neuropathic (Woolf, 2004). The dynamic interplay between inflammation pathways, pain sensation, and oxidative stress is demonstrated in Figure 1. Although several medications effectively reduce pain, they often come with significant side effects. Opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antidepressants, and anticonvulsants are commonly used to treat chronic and/or acute pain but are associated with side effects such as hypersensitivity, gastrointestinal problems, abdominal pain, nervousness, and hepato-renal toxicity (Beal and Wallace, 2016). COX-2-selective NSAIDs are associated with a reduced risk of NSAID-induced ulcers and gastrointestinal complications (Emery *et al*., 1999), but their use increases the risk of myocardial infarction (Vonkeman and van de Laar, 2010). Consequently, nutritional supplements, including trace minerals, vitamins, and herbal products, are increasingly utilized for pain and inflammation treatment due to their relatively lower side effect profiles compared to pharmaceuticals. Co-micronized mixtures of palmitoylethanolamide (PEA) with natural antioxidants such as astaxanthin have been developed for use in alleviating inflammatory pain in humans and small animals. Additionally, mixed persistent pain, which involves both inflammatory and neuropathic pain processing mechanisms, has been found to benefit from dietary supplementation with PEA and astaxanthin. The mechanisms of action underlying these benefits are discussed in this review.

Bioactive Compounds in Nutraceuticals

Nutraceutical is a combination of the terms 'nutrition' and 'pharmaceutical.' It includes products derived from herbs, nutrients, specific diets, foods, and beverages that are used not only for nutritional purposes but also for medicinal benefits (Kalra,

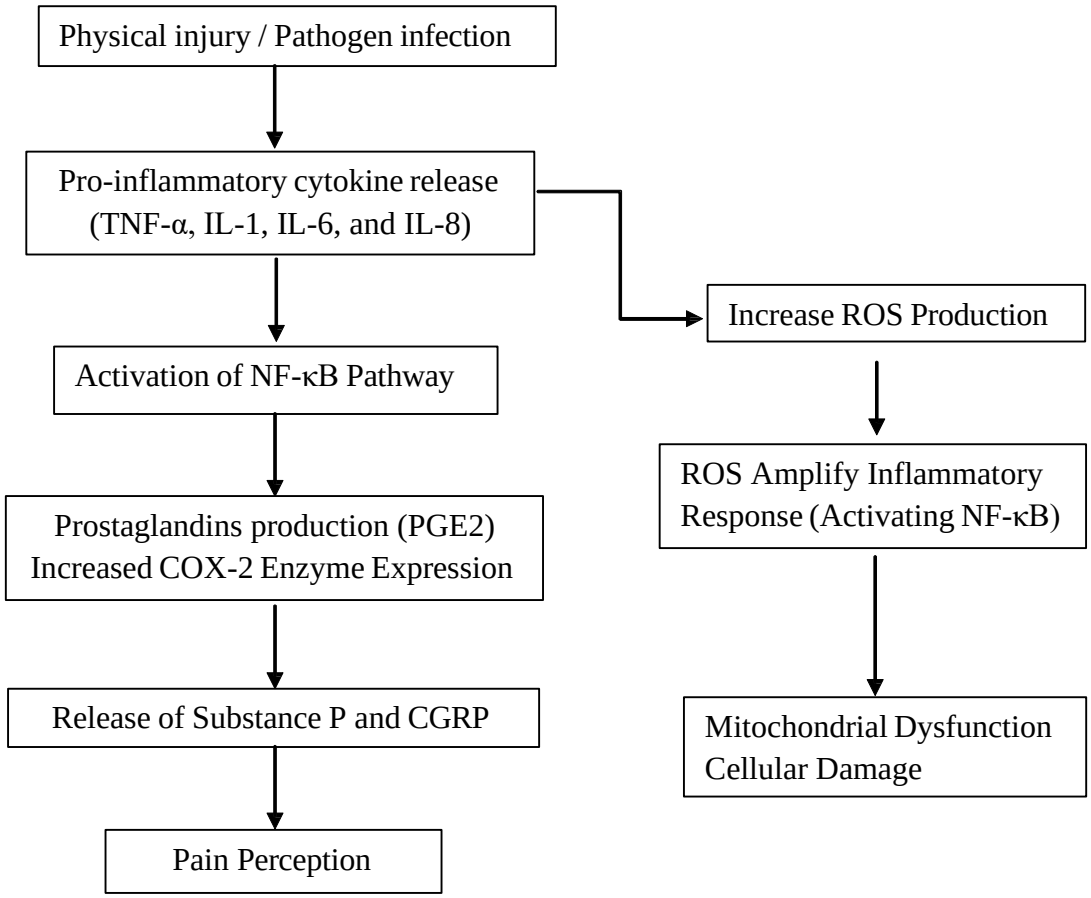

Fig. 1: Interplay of Pain, Inflammation Pathways, and Oxidative Stress (CGRP: Calcitonin gene-related peptide)

2003). Nutraceuticals encompass nutrient-derived bioactive compounds, including fatty acids, lipid molecules, fat-soluble vitamins (D and E), amino acids (arginine, glutamine, and glycine), carotenoids, polyphenolic compounds (flavonoids and phenolic acid) and spices (curcumin) (AlAli *et al*., 2021).
Among vitamins, the vitamin B complex was explored as a potential treatment in a femoral nerve injury rat model (Ehmedah *et al*., 2020). Similarly, Vitamin D stimulates the production of antimicrobial peptides, while Vitamin C is considered an antiviral and anti-inflammatory agent due to its ability to boost immunity (Bae and Kim, 2020).

Oxidative stress, an imbalance between free radicals and antioxidants, plays a significant role in pain and inflammation. Following painful stimuli, numerous intracellular pathways are activated, resulting in the generation of free radicals, reactive oxygen species (ROS), and the activation of inflammatory cytokines. These processes collectively lead to oxidative stress and cellular damage. Antioxidants like superoxide dismutase (SODs), glutathione peroxidase, and catalase (CAT) remove free radicals by converting harmful oxidative products into hydrogen peroxide (H_2O_2) and water. Nutraceuticals, with their antioxidant properties, may help control oxidative stress and inflammation associated with pain (Ilari *et al*., 2022). These nutraceuticals include low-molecular-weight compounds such as vitamins (especially C and E), plant-derived polyphenols, glutamine, glutathione, carotenoids (lycopene and β-carotene), quercetin, resveratrol, and palmitoylethanolamide (López-Gómez *et al*., 2021). Resveratrol, a phytoalexin and naturally occurring polyphenol compound primarily found in berries

and grapes, is produced by many plants when they are infected by pathogens or physically harmed by cutting, crushing, or ultraviolet radiation (Fremont and Lucie, 2000). It is available as a dietary supplement and is rich in antioxidants and anti-inflammatory compounds. Resveratrol regulates the inflammatory response through various signaling pathways, including the arachidonic acid, NF-κB, MAPK, activator protein (AP)-1 transcription factor, and antioxidant defense pathways (Meng *et al.*, 2021).

Curcumin has been used to treat chronic inflammatory diseases like arthritis (Kloesch *et al*., 2013), and its liposomal formulations hold promise as potential treatments for canine osteoarthritis (Rasool *et al*., 2024). Furthermore, co-micronizing palmitoylethanolamide (PEA) with curcumin has been shown to significantly reduce cartilage damage, radiographic deterioration, and osteoarthritis pain (Miolo *et al*., 2018).

Carotenoids, including β-carotene and lycopene, are essential nutrients that provide anti-inflammatory benefits. β carotene, a provitamin A, has been studied for its potential to alleviate chronic pain and inflammation. Its lipophilic properties enable it to localize in lipoproteins and cell membranes (Mohseni *et al*., 2009). Bae *et al*. (2021) confirmed β-carotene as a potential treatment to prevent *Helicobacter pylori* (*H. pylori*)-induced inflammation. In vitro studies demonstrated its ability to inhibit the *H. pylori*-induced activation of MAPKs and AP-1, as well as the expression of matrix metalloproteinase-10 and cell invasion. Lycopene, a lipophilic carotenoid hydrocarbon pigment similar to beta-carotene, is found in red, pink, and orange fruits and vegetables. Its anti-inflammatory effects stem from its lipophilic nature, which allows it to closely interact with cell membranes, regulating inflammatory mediator signaling pathways, and activating the expression of antioxidant genes (Khan *et al*., 2021). Additionally, Choi *et al*. (2021) demonstrated that lycopene, as an antioxidant, could inhibit cytokine expression induced by house dust mites, possibly by suppressing the activation of toll-like receptor 4 and reducing intracellular and mitochondrial oxidative stress in respiratory epithelial cells.

Role of Astaxanthin in Pain and Inflammation

Astaxanthin is a lipid-soluble, red-orange oxycarotenoid nutraceutical compound (Zheng *et al*., 2013) with potent antioxidant, anti-inflammatory, neuroprotective, and reno- and hepato-protective properties (Davinelli *et al*., 2018; Galasso *et al*., 2021). It alleviates chronic and acute inflammation in various diseases, including neurodegenerative disorders, diabetes, gastrointestinal disease, renal inflammation, as well as skin and eye diseases (Chang and Xiong, 2020). It is especially abundant in marine creatures such as lobsters, shrimp, trout, and salmon (Bjerkeng *et al*., 2007).

Astaxanthin has been found to attenuate many inflammatory biomarkers through multiple signaling pathways, including phosphatidylinositol-3-kinase/ protein kinase B (Akt), Nuclear factor erythroid 2-related factor 2 (NRF2), NF-κB, extracellular-signal-regulated kinase, c-Jun N-terminal kinases, p38 MAPK, and the Janus kinase 2/signal transducer and activator of transcription 3 pathways. It diminishes the expression of COX-2, iNOS, and ICAM-1 proteins in streptozotocin (STZ)-induced diabetic rats, leading to reduced inflammation (Park *et al*., 2015). Additionally, it decreases the gene expression of pro-inflammatory cytokines (Kishimoto *et al*., 2010).

Studies have demonstrated that astaxanthin suppresses inflammation induced by excessive physical activity (Baralic *et al*., 2015). Astaxanthin supplementation in mice with ovalbumin-induced allergic asthma alleviated airway inflammation, reduced IgE and IgG1 levels, and modulated the Th1/ Th2 imbalance by preventing the production of IL-4 and IL-5 Th2 cytokines while elevating the production of Interferon-gamma (IFN-γ) Th1 cytokine (Hwang *et al*., 2017). IFN-γ is a cytokine associated with anti-proliferation, pro-apoptosis, anti-tumor, auto-inflammation, and autoimmune disorders (Schoenborn and Wilson, 2007; Castro *et al*., 2018). In a carrageenan-induced pain and inflammation model, astaxanthin showed therapeutic efficacy, accompanied by decreased oxidative stress

(Kuedo *et al*., 2016; Sharma *et al*., 2018).

Astaxanthin (AST) has been shown to attenuate pruritus and dermatitis by suppressing eotaxin, macrophage migration inhibitory factor (MIF), IL-4, and IL-5 mRNA and protein expressions (Yoshihisa *et al*., 2016). Atopic dermatitis (AD) is a chronic or relapsing inflammatory skin disease characterized by the activation of toll-like receptors and protease-activated receptor-2 (PAR-2) in keratinocytes, which induces the production of cytokines and chemokines (Boguniewicz *et al*., 2011; Maeda *et al*., 2013). The anti-inflammatory effects of AST mediate this skin protection (Yoshihisa *et al*., 2016; Park *et al*., 2018). AST treatment can diminish the severity of dermatitis in mouse models of AD by modulating inflammatory parameters (Yoshihisa *et al*., 2016).

Astaxanthin (AST) administration has demonstrated efficacy in enhancing renal function by mitigating inflammation and reducing the generation of reactive oxygen species (ROS). These beneficial effects were attributed to the upregulation of Nrf2 expression and the suppression of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) (Liu *et al*., 2015).

Aligned with the preceding research, Astaxanthin (AST), known for its multifaceted pharmacological actions, holds potential as a therapeutic agent for managing diverse inflammatory diseases.

Palmitoylethanolamide (PEA): Mechanisms and Benefits

Palmitoylethanolamide (PEA), a naturally occurring bioactive lipid compound, is a derivative of N-acylethanolamine, produced on-demand by various cell types, including mast cells, astrocytes, and microglia in response to stress and tissue damage (Bisogno *et al*., 1997; Muccioli *et al*., 2008; Walter *et al*., 2002). PEA is naturally present in a variety of food sources, including egg yolk, soybean lecithin, and bovine milk. It is also found in nearly all mammalian body fluids (such as reproductive fluids and synovial fluid), as well as in the eyes, gastrointestinal tract, spinal cord, and various tissues, including subcutaneous adipose tissue and skin. In these locations, PEA is synthesized, released, and degraded (Esposito and Cuzzocrea, 2013). PEA exhibits significant analgesic, anti-inflammatory, and neuroprotective effects, acting on various molecular targets, including immune cells (Hoareau *et al*., 2006). The autoprotective function of PEA was first suggested in dogs, where it was discovered that the canine myocardium produces PEA in response to ischemic injury (Natarajan *et al*., 1981; Epps *et al*., 1979). Additionally, the canine brain has the biosynthetic and degradative mechanisms for PEA (Natarajan *et al*., 1984). PEA, a cannabimimetic compound, reduces pain through various endocannabinoid-driven activities (LoVerme *et al*., 2005). Its analgesic effects may be attributed to its agonism of peroxisome proliferator-activated receptor-α (PPAR-α) (Calignano *et al*., 1998). PEA also reduces inflammation by inhibiting pro-inflammatory enzymes such as COX, eNOS, and iNOS (Costa *et al*., 2002) and by reducing mast cell activation (Mazzari *et al*., 1996; Calignano *et al*., 2001). The anti-inflammatory and protective activities of PEA have been demonstrated in several models of inflammation, such as carrageenan-induced paw edema, adjuvant-induced arthritis, tuberculin hypersensitivity, and ischemia-reperfusion injury (Di Paola *et al*., 2012a, 2012b; Esposito and Cuzzocrea, 2013). Additionally, PEA exhibits anti-inflammatory effects by inhibiting TNF-α levels in the serum of mice treated with LPS and in human adipocytes (Hoareau *et al*., 2009).

Palmitoylethanolamide (PEA) is synthesized from a glycerophospholipid precursor in the cell membrane and degraded by two amidases: fatty acid amide hydrolase (FAAH) located in the cell membrane and N-acylethanolamine acid amidase (NAAA) located in the lysosome (Hussain *et al*., 2017; Tsuboi *et al*., 2018; Sun *et al*., 2004; Ueda *et al*., 2010). PEA metabolism can be disrupted under certain conditions, such as chronic inflammatory disorders (Alhouayek and Muccioli, 2014). Significant decrease in local PEA levels have been observed in various chronic pain models (Petrosino *et al*., 2007; Charrua *et al*., 2020; Zhou *et al*., 2019). Normalizing PEA levels through the inhibition of

its degradative pathways can therefore reduce inflammation and pain (Zhou *et al*., 2019). PEA levels may increase in response to cell damage, as demonstrated in epidermal cells exposed to UV irradiation (Berdyshev *et al*., 2000), the lesional skin of dogs with atopic dermatitis (Abramo *et al*., 2014), and the colons of dogs with chronic enteropathy (Pengo *et al*., 2012) to limit disease severity. Consequently, exogenous administration of PEA to supplement the body's own supply is considered a promising therapeutic approach (Skaper *et al*., 2014). The absorption of lipophilic substances is inversely proportional to the size of their particles (Takano *et al*., 2008). Consequently, particle size reduction (such as in micro-PEA), either alone or in combination with adjuvants (typically antioxidants), improves pharmacokinetics and bioavailability. This leads to superior clinical effects and enhanced functional properties following oral administration (Takano *et al*., 2008; Dhiman *et al*., 2021). Micro-PEA down-regulates allergic hyperactivity, significantly reducing mediator release (e.g., degranulation) and lowering histamine levels (Cerrato *et al*., 2010; Abramo *et al*., 2017). Consequently, it can benefit patients with hypersensitive skin disorders. Studies have shown that dietary supplementation with micro-PEA (15 mg/kg daily for 45 days) significantly decreased the severity of clinical signs such as pruritus and erythema in both food-induced and non-food-induced atopic dermatitis (Waisglass *et al*., 2009). Similarly, dietary supplementation with micronized PEA has also been beneficial for cats, improving skin signs and symptoms in those with eosinophilic plaque and eosinophilic granuloma (Scarampella *et al*., 2001). Additionally, dogs supplemented for 4 weeks with a complementary feed containing PEA co-ultramicronized with the natural antioxidant quercetin (PEA-q, 24 mg/kg body weight) experienced a reduction in the severity of chronic pain due to osteoarthritis or persistent lameness (Vezzoni *et al*., 2018).

Thus, the protective effects of PEA and AST may be due to the inhibition of the inflammatory (NF-κB) pathway and the reduction of reactive oxygen species generation, thereby preventing cellular damage and alleviating pain. Therefore, these agents can be used in the treatment of several inflammatory disorders.

CONCLUSION

Nutraceutical supplements, particularly palmitoylethanolamide in combination with antioxidants such as astaxanthin, show promise in managing pain and inflammation and may offer several advantages over currently available treatments. Although there are limited clinical reports regarding the protective effects of palmitoylethanolamide and astaxanthin against inflammatory diseases, these nutraceuticals should be further characterized for their properties as a potential therapeutic strategy in combating inflammatory diseases.

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