

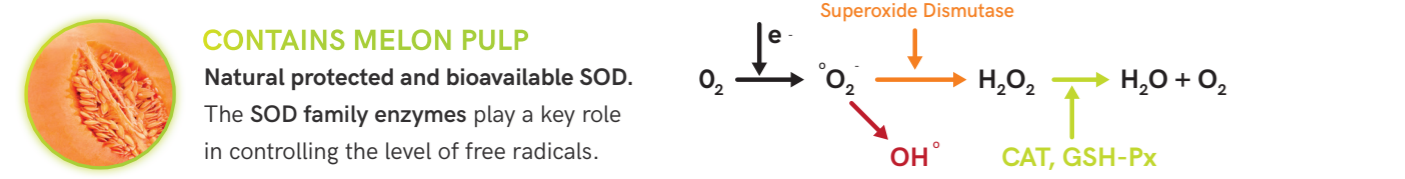
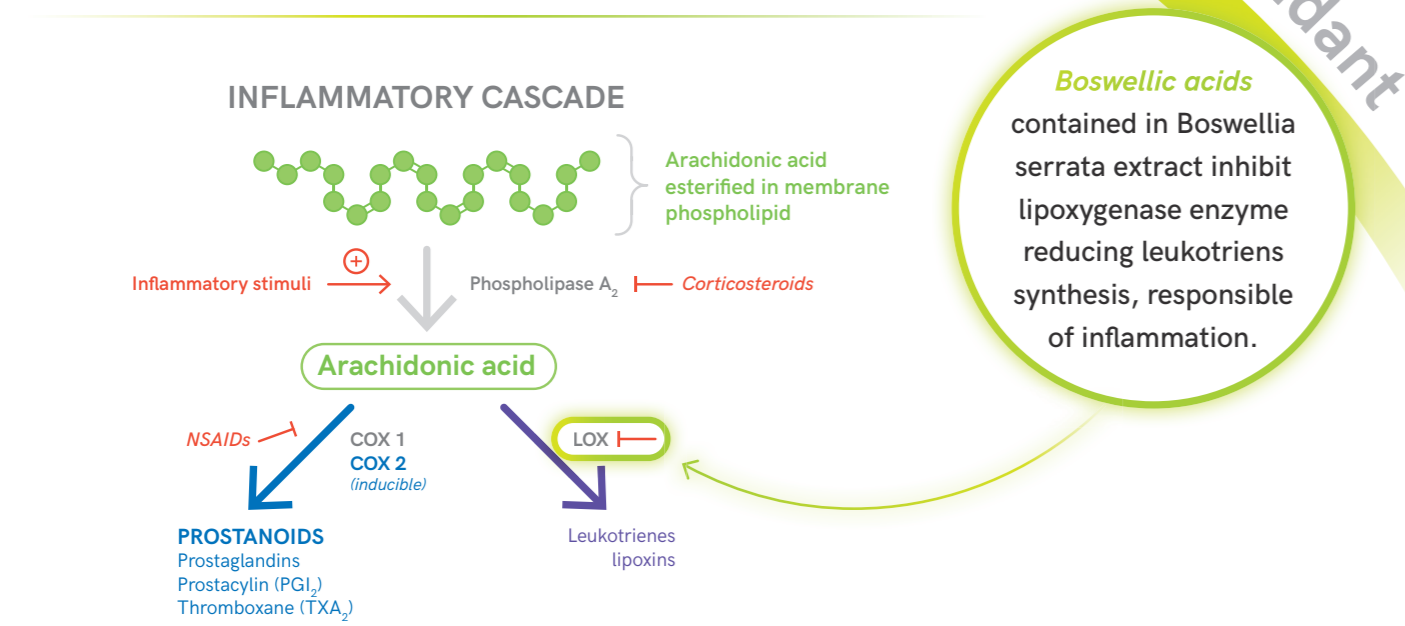
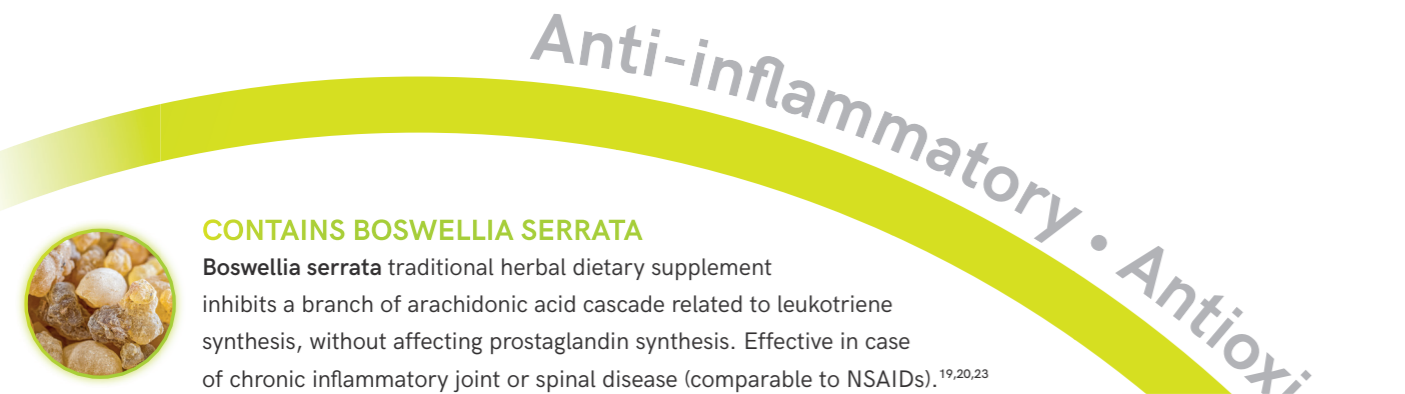
Evexia HF

PEA exerts antinociceptive effect, neuroprotective effects, anti-inflammatory activity, analgesic action, neuromodulatory activity in CNS^{8,13,14,21}.

PALMITOYLETHANOLAMIDE ENDOGENOUS PRODUCTION INCREASES WITH STRESS FORM

ACTIONS OF EXOGENOUS PALMITOYLETHANOLAMIDE

Peripheral tissue-inflammation	Anti-Inflammation
Neuroinflammation	Neuroprotection
Pain	Pain relief



Evexia HF

High content of Palmitoylethanolamide (PEA) and Boswellia serrata



COMPOSITION

Brewers' yeasts, inactivated, Palmitoylethanolamide (PEA) 14%, Dicalcium phosphate, Magnesium stearate, Mono- and diglycerides of fatty acids esterified with organic acids (Glyceryl dibehenate), Vegetable oil (Palm oil), Products and co-products from processing fresh fruits and vegetables (Melon)

ADDITIVES PER KG

Stabilisers: Microcrystalline cellulose E460 387,500 mg **Emulsifiers:** Lecithins 1c322i 41,250 mg **Sensory additives:** Boswellia serrata Roxb. Ex Colebr.: Olibanum extract 43,750 mg **Anti-caking agents:** Colloidal silica E551b 31,870 mg **Amino acids:** L-Arginine 3c361 12,500 mg **Vitamins:** Vitamin E 3a700 10,000 mg

ANALYTICAL CONSTITUENTS

Crude protein 15.0 % - Crude fibres 47.0 % - Crude fat 13.0 % - Crude ash 11.0 % - Ash insoluble in HCl 7.0% - Moisture content 4.0 %

INSTRUCTION FOR PROPER USE

Evexia HF is a complementary feed for dogs and cats.

Administer Evexia HF directly into the mouth or mix with food according the following daily quantities:

Weight (kg)	Tabs per day
0-7.5 kg b.w.	1 TAB
7.5-15 kg b.w.	2 TABS
15-22.5 kg b.w.	3 TABS
22.5-30 kg b.w.	4 TABS
30-40 kg b.w.	5 TABS
40-60 kg b.w.	6 TABS

Drinking water available for the animal is recommended.

The minimum storage life means the period during which, under proper storage conditions the feed retains its properties. Keep the bottle closed after use. Keep in a dry place and protect from sunlight and heat sources before and after opening. Not for human consumption.

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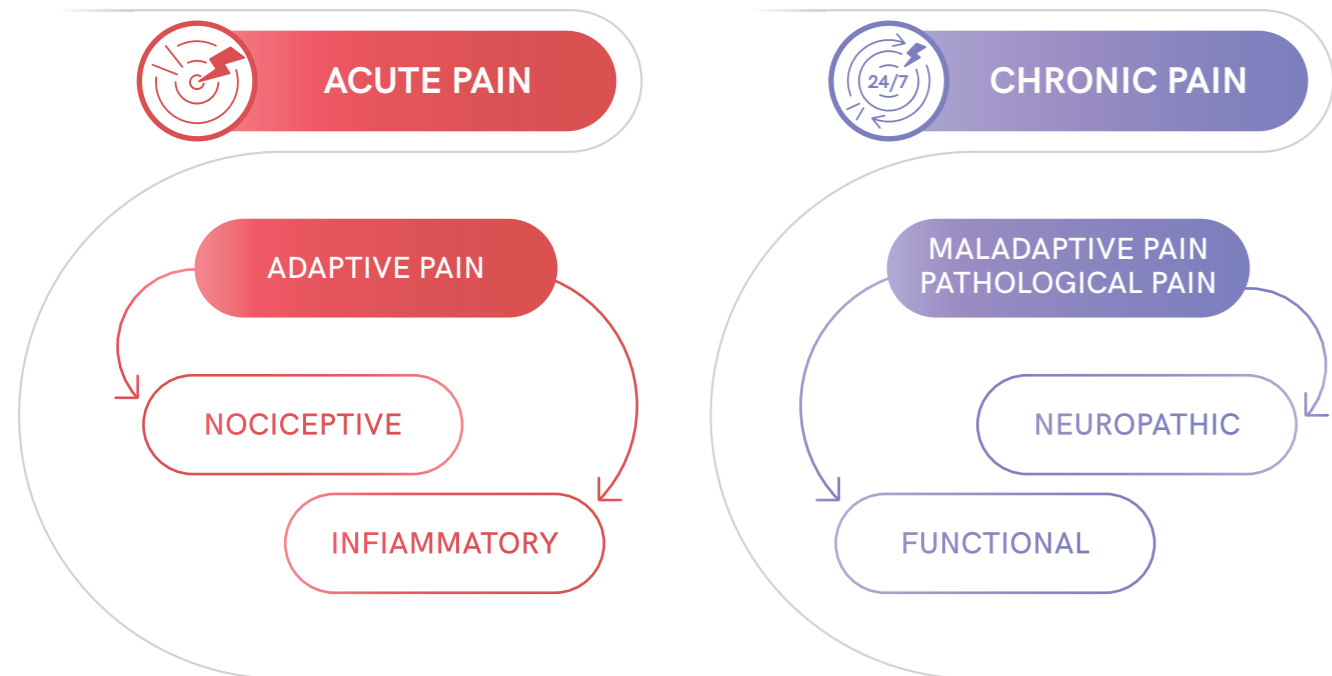
Chronic pain is multifactorial

Pain has protective biological functions because it represents an early warning system and triggers a series of protective reflexes, and as such is defined physiological or adaptive pain²².

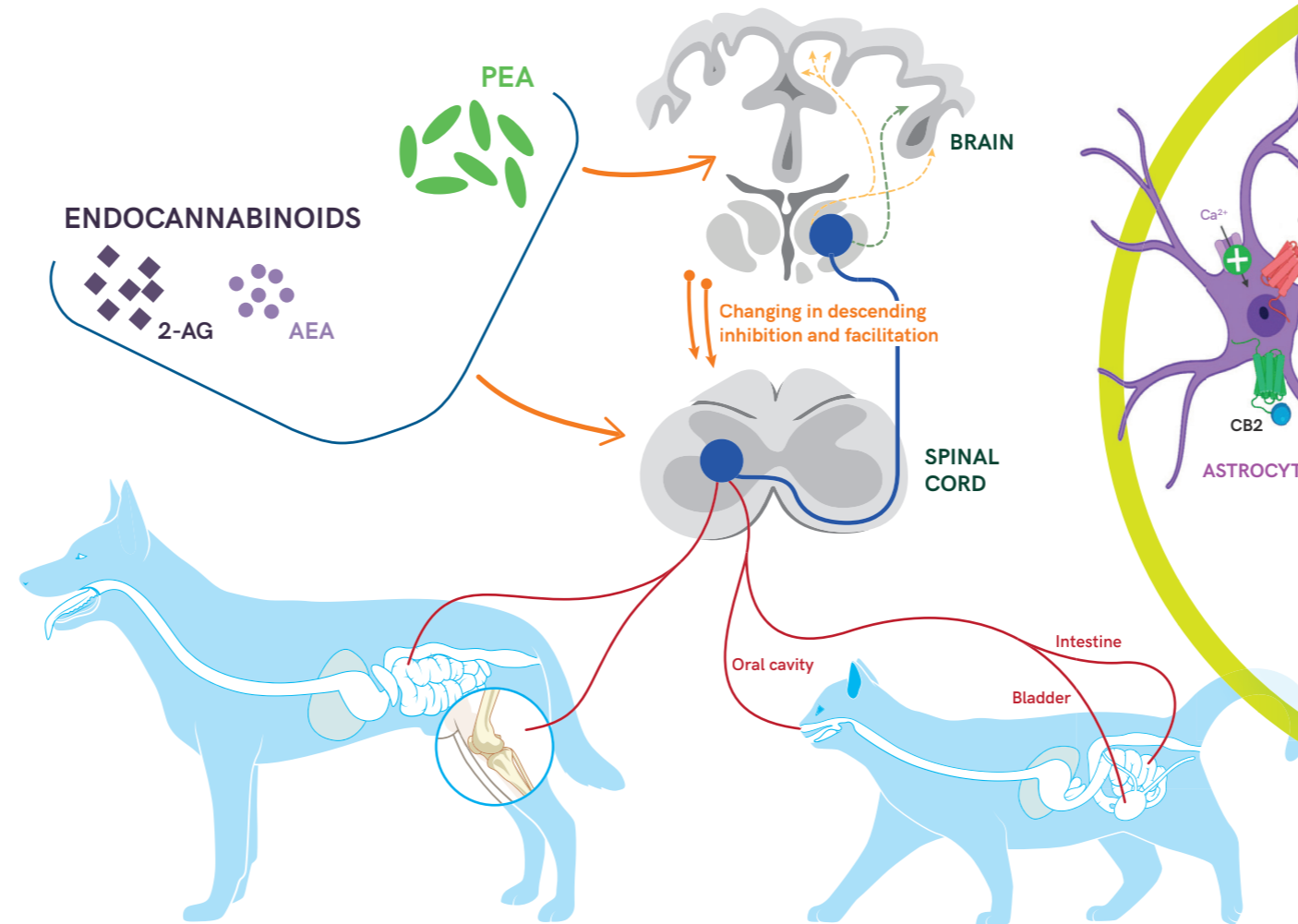
Instead, pain that persist for long time can result in changes in the pain transmission system at multiple levels:

- Triggers metabolic stress reactions
- Enhances neuroendocrine reactions
- Changes organic functions and it is called pathological or maladaptive pain

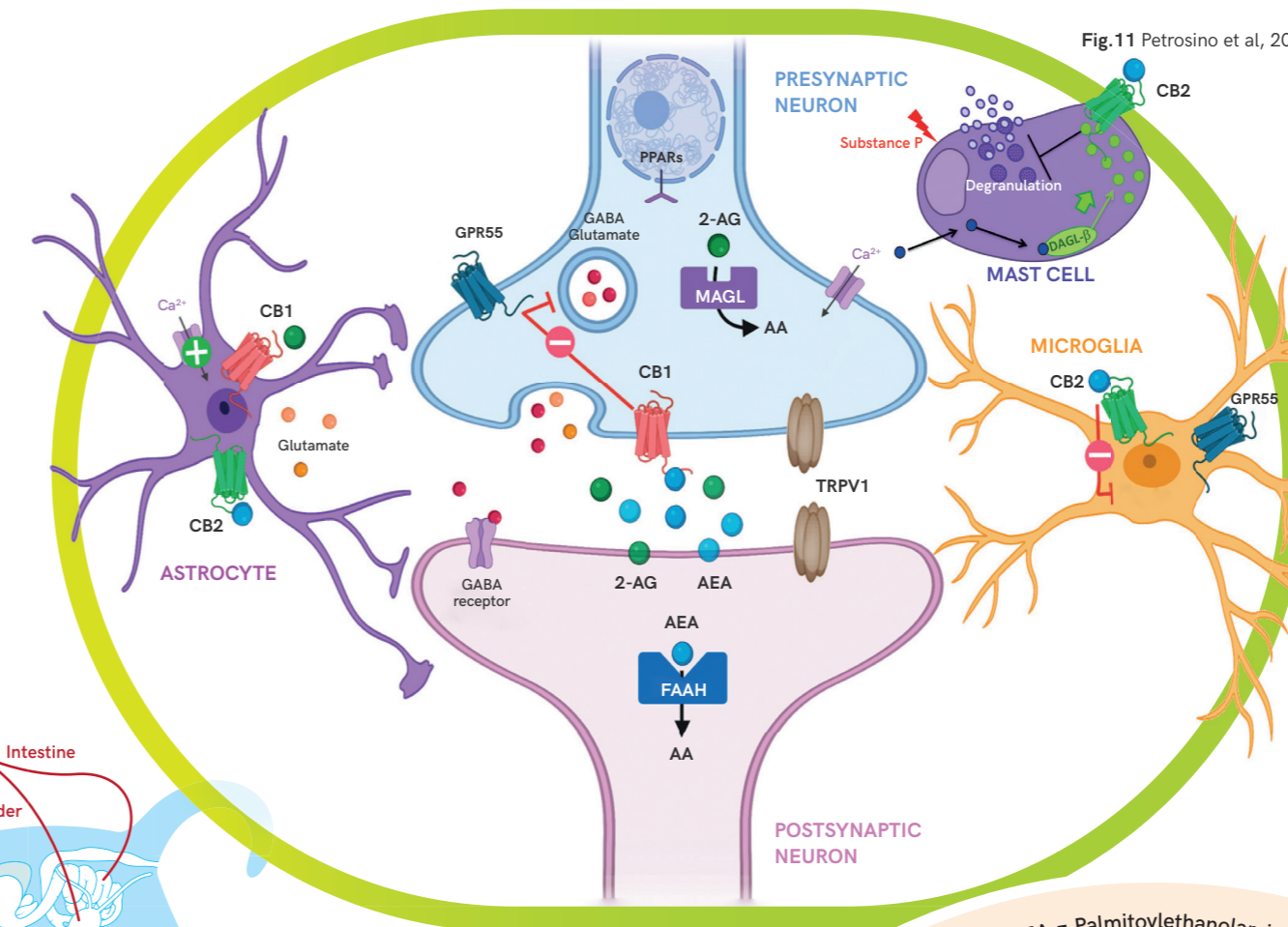
CLINICAL PAIN IS OFTEN A MIXTURE OF ALL "TYPES" OF PAIN²⁵



Pain pathways



Palmitoylethanolamide PEA



N-Palmitoylethanolamide (PEA) is an **endocannabinoid-like ethanolamines** mediator belonging to the class of the N-acyl ethanolamine phospholipids recognised as an **endogenous member of the endocannabinoid system (ECS)**. PEA can induce its biological effects by acting on several molecular targets in both central and peripheral nervous systems. These multiple mechanisms of action clearly differentiate PEA from classic anti-inflammatory drugs and are attributed to the compound that has quite unique anti(neuro) inflammatory properties^{3,13,17}.

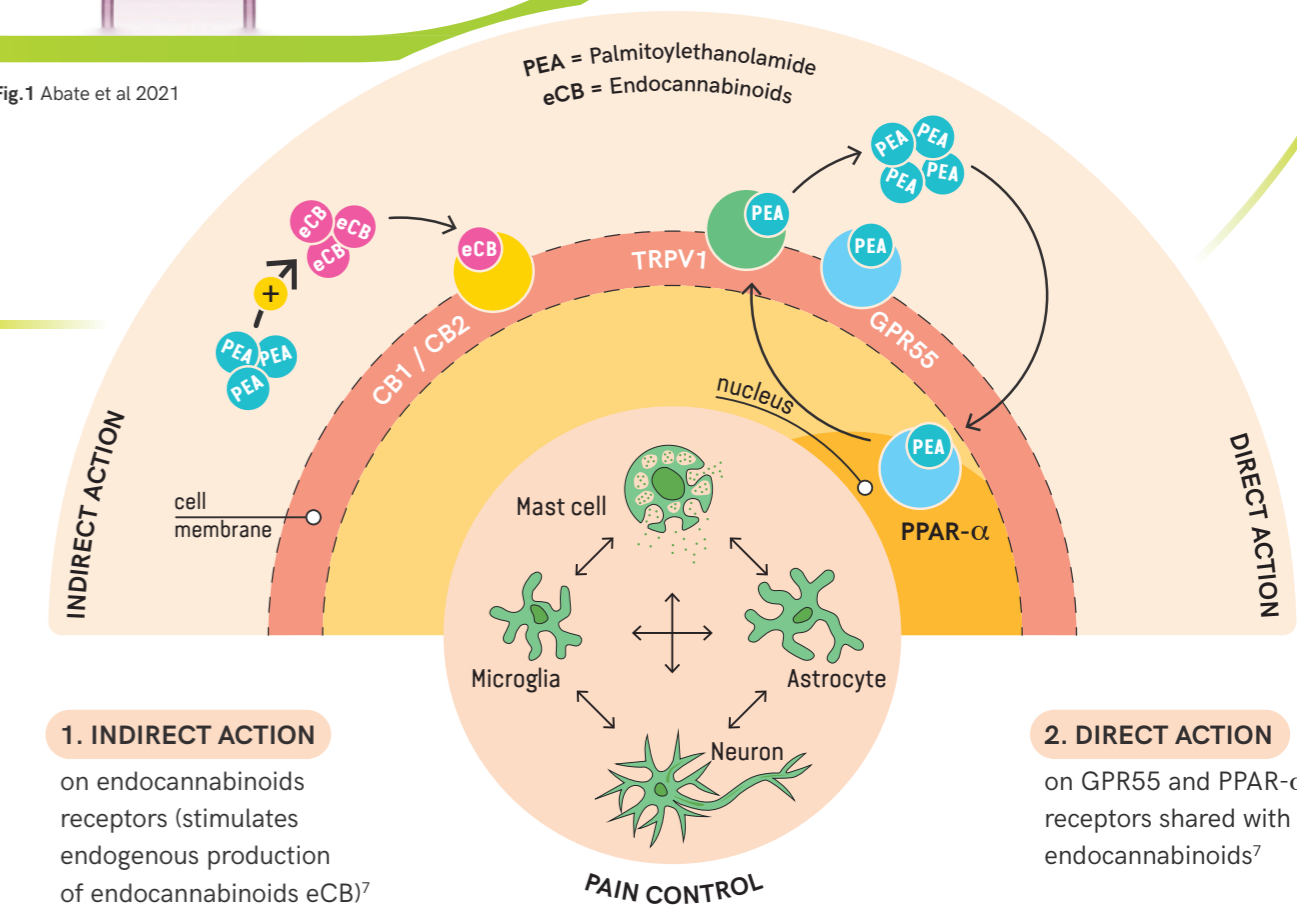
Fig.1 Abate et al 2021

Most common causes of chronic pain^{7,12}

<p>Osteoarthritis (OA)</p>	<p>Maladaptive chronic pain not related to OA or cancer</p> <p>CNS lesions, PNS lesions eg. Diabetes-induced neuropathy, Persistent Postsurgical Pain, Feline Orofacial Pain Syndrome</p>
<p>Chronic or chronic-active inflammatory pain not related to OA</p> <p>chronic visceral disorders eg. Intestinal Bowel Disease, idiopathic cystitis, pancreatitis</p>	<p>Cancer pain</p> <p>Osteosarcoma, oral squamous carcinoma and cancer-associated therapy eg. chemotherapy-induced neuropathy, radiation-induced skin burns</p>

The mode of action of PEA include a possible local **autocoid-like mediator activity** regulating mast-cell activity and putative activation of **cannabinoids and vanilloid TRPV1 receptors** via "entourage" effects^{5,10,17}.

ALIA (Autocoid Local Injury Antagonism) mechanism represents the way to **down-regulate non-neuronal cells** via multiple receptor mechanisms. PEA activate (or desensitises) directly or indirectly (entourage effect) endocannabinoid receptors (CB2), vanilloid receptors (capsaicin receptor TRPV1) and nuclear receptor of inflammation (PPAR-α)^{17,18,24}.



1. INDIRECT ACTION on endocannabinoid receptors (stimulates endogenous production of endocannabinoids eCB)⁷

2. DIRECT ACTION on GPR55 and PPAR-α receptors shared with endocannabinoids⁷