

Evexia

Contains Hemp Oil



Complementary feed for dogs and cats

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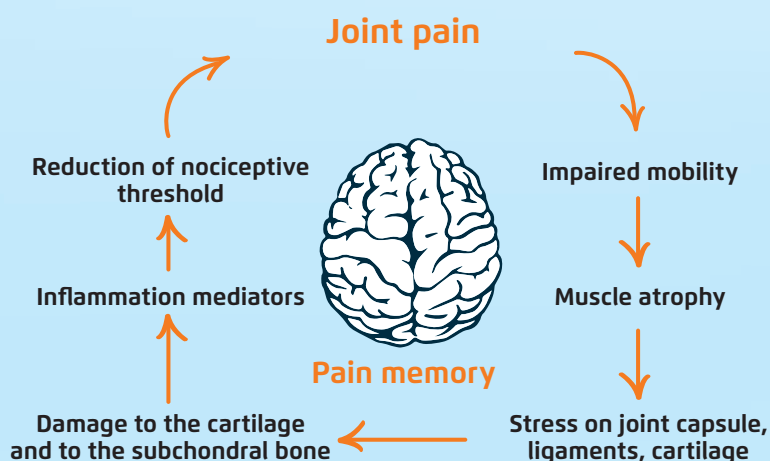
Candioli
PHARMA

CHRONIC ORTHOPEDIC 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 pain**²².

Instead, if the pain persists for a long time:

- **enhances neuroendocrine reactions,**
 - **triggers metabolic stress reactions,**
 - **changes organic functions**
- ...and is called **pathological pain**²²



Chronic orthopaedic pain²² is, at least in part, the consequence of **nociceptive stimulation of** ^{9,10,11,14,22}

- **joint capsule**
- **synovial membrane**
- **ligaments and subchondral bone**

activated by inflammatory cytokines (PG, LT, IL, TNF- α) and free radicals (NO) ^{6,10,11,19,20}

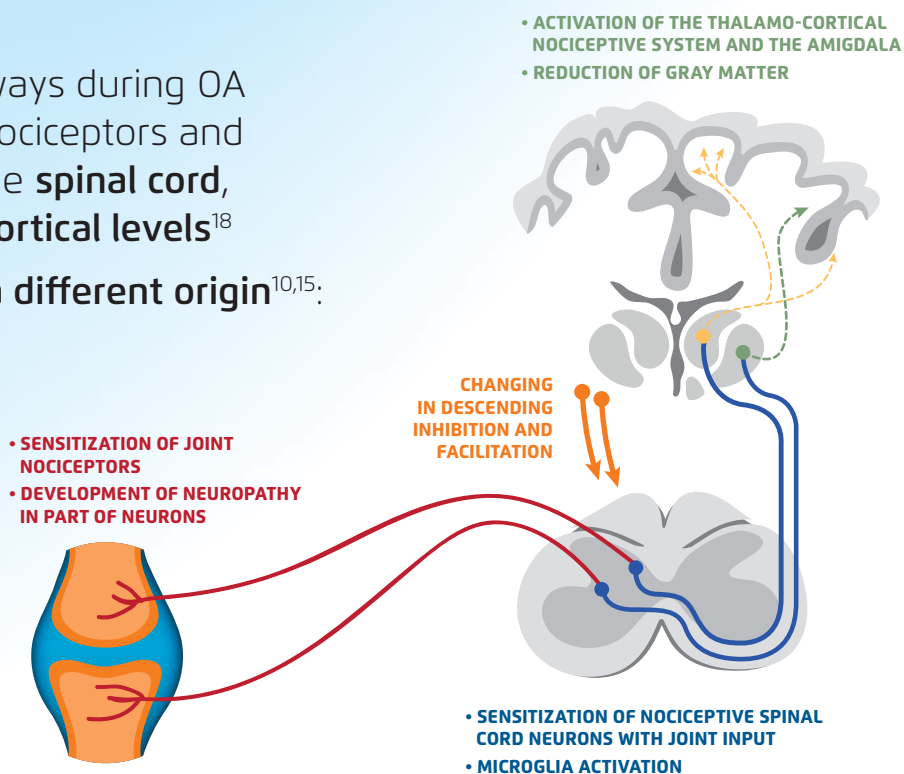
Fig. 1 Self-supporting musculoskeletal system pain development cycle. (from Tacke S. 2011)

Sensitization of pain pathways during OA involves changes in joint nociceptors and nociceptive variations at the **spinal cord**, **encephalon**, and **thalamocortical levels**¹⁸

Therefore, pain in OA **has a different origin**^{10,15}:

- **inflammatory**
- **nociceptive**
- **neuropathic**

Fig. 2 Diagram of the articular nociceptive system and at different neuronal processes at different neuraxis levels¹⁹



ENDOCANNABINOID SYSTEM MODULATES

The **Endocannabinoid System (ECS)** is a complex biological mechanism of neurological signaling composed of receptors, constituent ligands and their inhibiting enzymes^{2,4,5,15,16}

Endocannabinoids (EC) are cannabinoids produced by the body. They are a family of bioactive lipids that activate cannabinoid receptors, modulating neural transmission and thus participating in the **regulation of different brain functions**¹²

The main ECS endogenous receptors are^{2,4,5,15}:

CB1

located mainly along the "pain pathway" at the peripheral neuron, spinal cord, and brain level

CB2

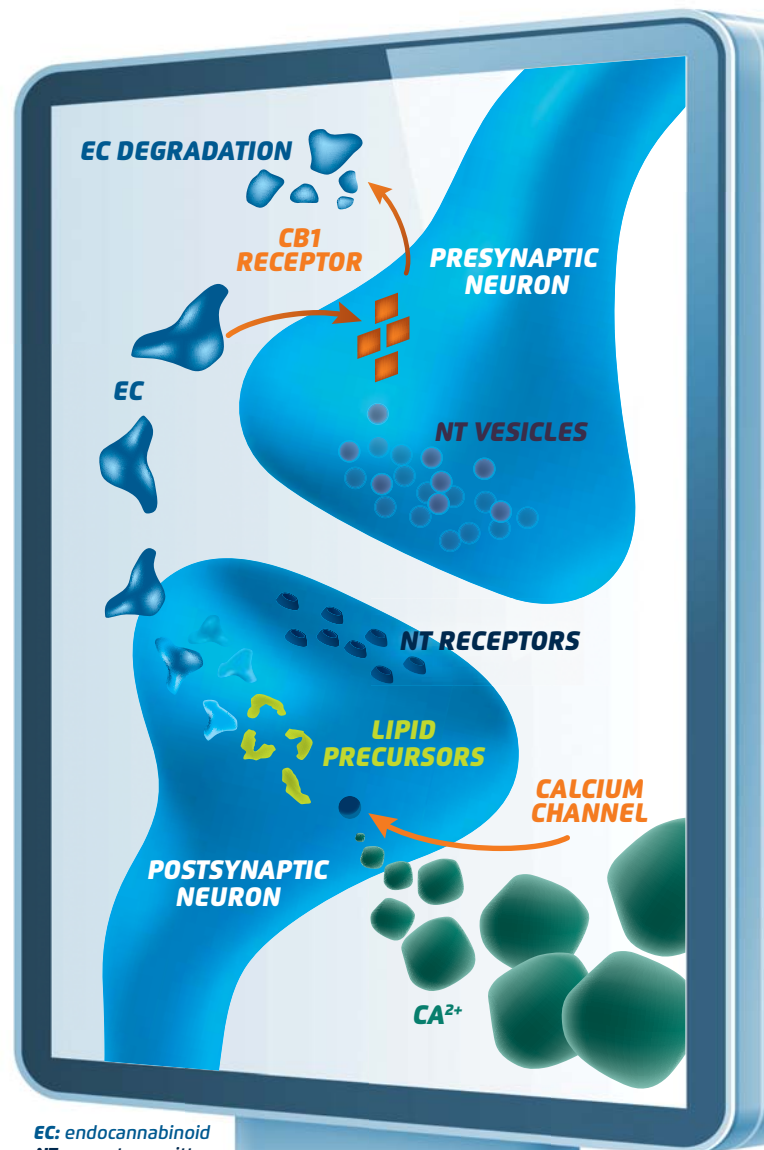
present in the central and peripheral nervous systems, and especially in the immune cells (macrophages, mast cells and glial cells, responsible for inflammatory pain)

PHYSIOLOGICAL ACTIONS

MEDIATED BY THE ACTIVATION OR INHIBITION OF ENDOCANNABINOID RECEPTORS⁴

- Antinociception
- Cognition and memory
- Locomotor activity
- Endocrine functions
- Temperature control and heart rate
- Nausea and vomiting
- Intraocular pressure
- Inflammation
- Immune recognition and antitumor effects

Exogenous cannabinoids such as phytocannabinoids, cannabidiol (CBD) and tetrahydrocannabinol (THC) contained in hemp oil (*Cannabis sativa*), interact with the endocannabinoid system (ECS) as CB1 and CB2 receptor agonists, miming the effects of endogenous cannabinoids^{2,4,12,15,16}, thus playing a role in homeostatic endogenous modulation of nociception¹²



AND REGULATES PAIN

Cannabidiol (CBD) contained in hemp oil naturally modulates the activity of the Endocannabinoid sensory system^{2,4,12,15,16}

Exogenous cannabinoids, including CBD, may provide varying degrees of analgesia in different types of pain, particularly in situations of hyperalgesia and inflammation^{4,7}.

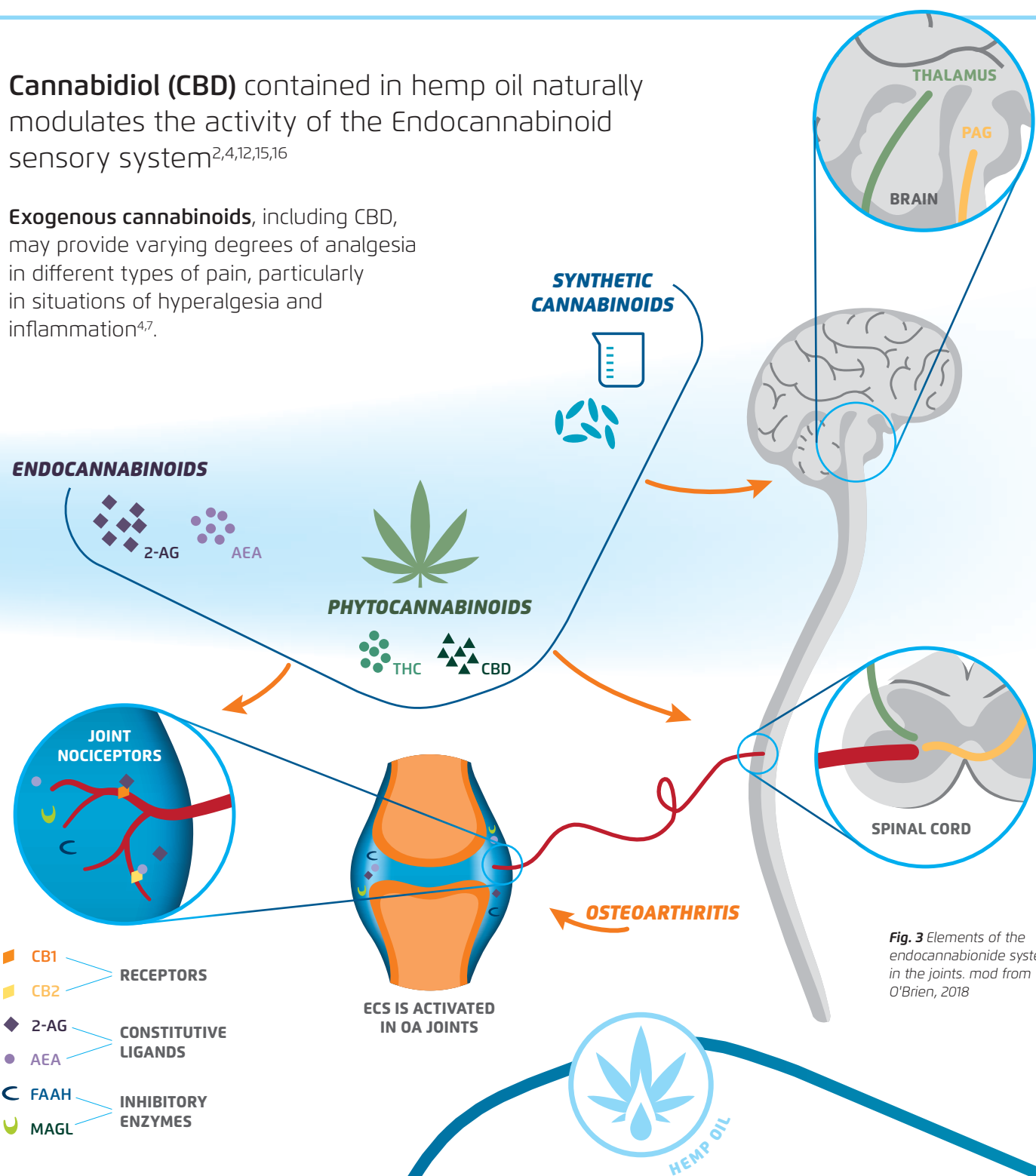


Fig. 3 Elements of the endocannabinoid system in the joints. mod from O'Brien, 2018

SAFETY

DAILY DOSES OF CBD UP TO 1500 MG ARE CONSIDERED SAFE IN HUMANS AS WELL AS ANIMALS¹³

Cannabidiol does not have the psychotropic effects of THC^{15,16}, and can be safely used for modulation of chronic neuropathic, inflammatory, and nociceptive pain, such as that caused by OA^{1,2,3,4,15,16}

SYNERGY

Prostaglandin and cyclooxygenase inhibitors interact with cannabinoids, **increasing the activity of CB1¹² endocannabinoid receptors**

Evexia INGREDIENTS:

The control of joints inflammation and oxidative damage is important in **the natural modulation of pain caused by OA**^{6,9,11,19,20}

CASPEROME®

EXTRACT OF
BOSWELLIA
PHYTOSOMIZED

4 times more bioavailable^{9,13} thanks to the patented lecithin delivery form (phytosome) technology  **indena®**

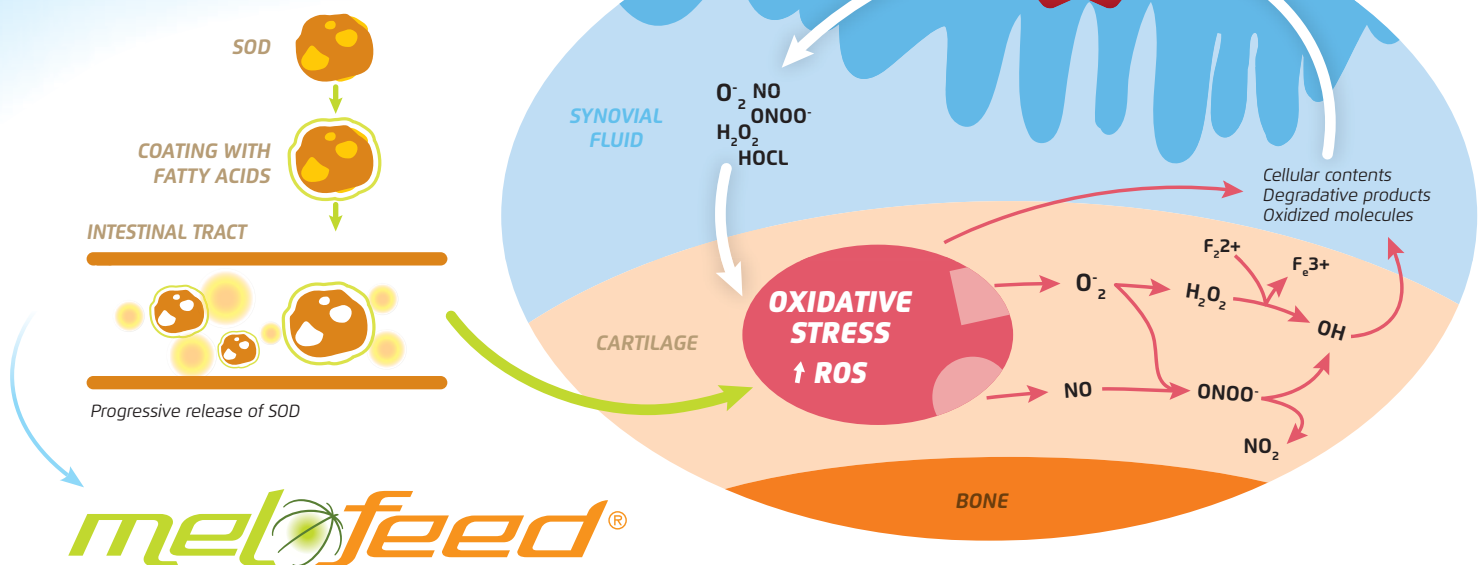
The Boswellia extract:

• Prevents inflammatory mediators synthesis (IL-1 β , TNF- α , PGE₂)²³

• Reduces oxidative damage²³

• Enhances the activity of antioxidant defense systems (GSH, SOD, Catalase)²³

Fig. 4 The implication of ROS in cartilage degradation and related synovium inflammatory reaction. H₂O₂: hydrogen peroxide; ONOO⁻: peroxynitrite; OH⁻: hydroxyl radical; O₂⁻: superoxide anion. from Henrotin 2003



melfeed®

Natural protected and bioavailable SOD

The **SOD family enzymes** play a key role in controlling the level of free radicals in the cartilage^{10,20}.

In OA animal cartilage (Guinea pigs), SOD2 (Mn-SOD) levels are **significantly reduced** even at an early stage²⁰, before the onset of cartilage erosions.

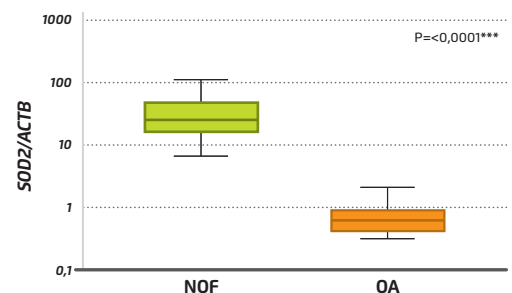
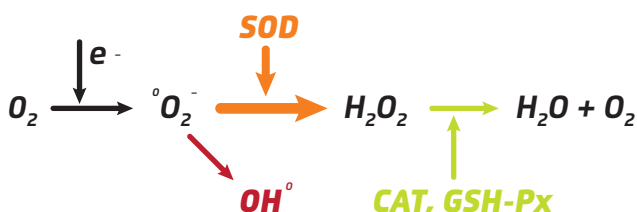


Fig. 5 Comparison of SOD gene expression between femoral neck cartilage (NOF9) and patients with osteoarthritis (OA), in relation to the ACTB gene. Values measured with RT-PCR on 12 +12 subjects: the lines inside the boxes represent the medians, the boxes show the 25th and 75th percentage, the lines outside the boxes show the maximum and minimum values. from Scott JL 2011 mod.

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Contains Hemp Oil



COMPOSITION

Yeasts [brewer's yeast], Hemp oil 3.0%, Magnesium stearate, Mono and diglycerides of fatty acids esterified with organic acids (glyceryl dibehenate), Products from the processing of plants (Melon) (*Melofeed), Product from the processing of plant (Hemp)

ADDITIVES PER KG

Emulsifiers, stabilising agents, thickeners and gelling agents: Microcrystalline cellulose E460 mg 412.930 - Lecithin 1c322 mg 42.500 Organoleptic additives: Boswellia serrata Roxb. ex Colebr.: Oliban extract (*Casperome®) mg 49.375 Anti-caking agents: Colloidal silica E551b mg 21.875 Amino acids, their salts, and analogues: L-Arginine mg 12,500 Preservatives: Butylhydroxytoluene (BHT) E321 mg 100

INSTRUCTIONS FOR PROPER USE

Evexia is a complementary feed for dogs and cats. The hemp oil contained in Evexia promotes the physiological maintenance of sensory function. Give Evexia to your pet directly in the mouth or mix it with the regular feed serving for a minimum period of 20 days according to the following daily amounts:

Tablets per day			
0-7.5 kg b.w.	1/2 tablet	22.5-30 kg b.w.	2 tablets
7.5-15 kg b.w.	1 tablet	30-40 kg b.w.	2½ tablets
15-22.5 kg b.w.	1½ tablets	40-60 kg b.w.	3 tablets

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