A.D. 1308 unipg
DIPARTIMENTO DI MEDICINA VETERINARIA

CeRiDA
Centro di Ricerca sul Dolore Animale

Cannabinoidi in Medicina veterinaria

Giorgia della Rocca

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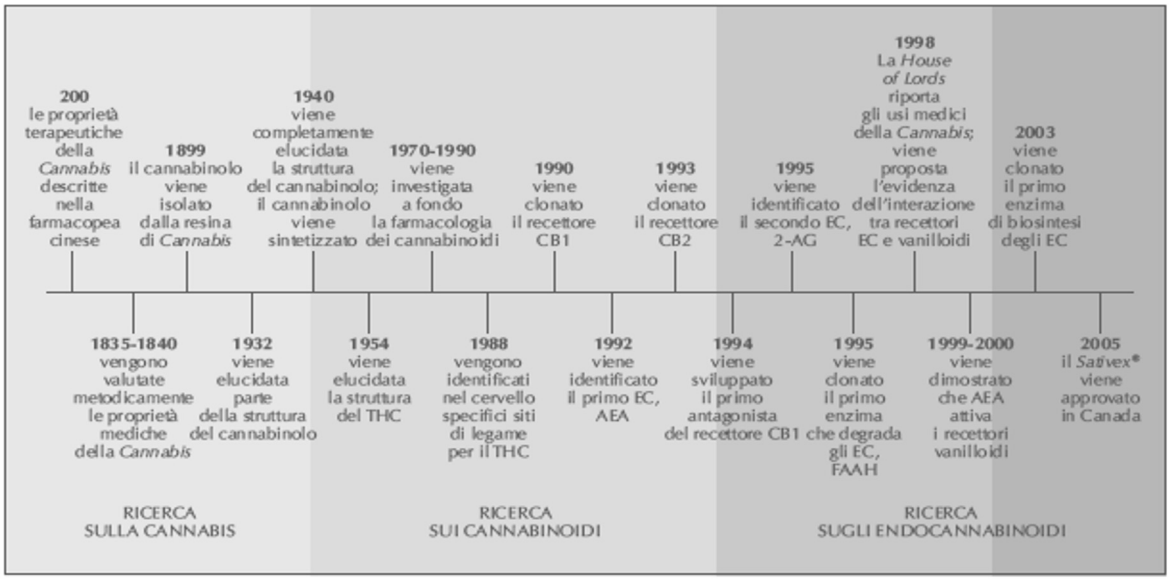
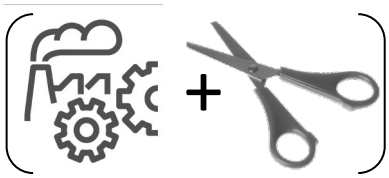
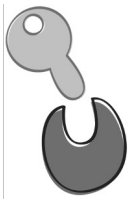
CANNABIS E SISTEMA ENDOCANNABINOIDE



2

COMPONENTI IL SISTEMA ENDOCANNABINOIDE (endocannabinoidoma)

LIGANDI	ENZIMI		RECETTORI
			
N-acil-etanolamidi (AEA, OEA, SEA, **PEA**) e N-acilgliceroli (2-AG)	**Biosintetici** (es. NAPE-PLD)	**Degradativi** (es. FAAH, NAAA, MAGL)	**CB1, CB2** TRPV1, GPR55, GPR119, PPAR-α ….

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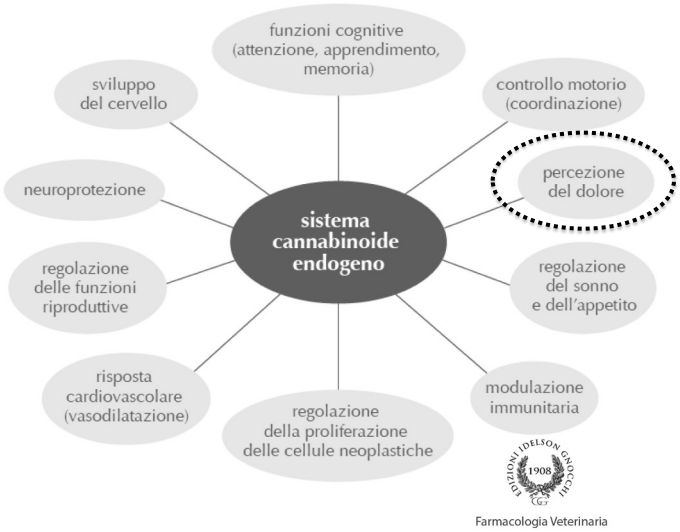
PRINCIPALI FUNZIONI DEL SISTEMA ENDOCANNABINOIDE NELLE NORMALI CONDIZIONI FISIOLOGICHE



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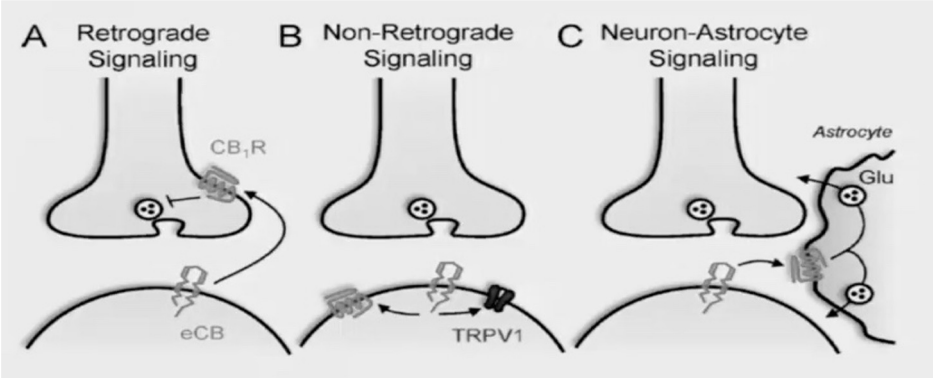
AZIONE DEGLI ENDOCANNABINOIDI

- Segnale retrogrado
- Segnale anterogrado (via TRPV1) - AEA
- Comunicazione neurone-glia



Castillo et al, Neuron 76, 4, 2012

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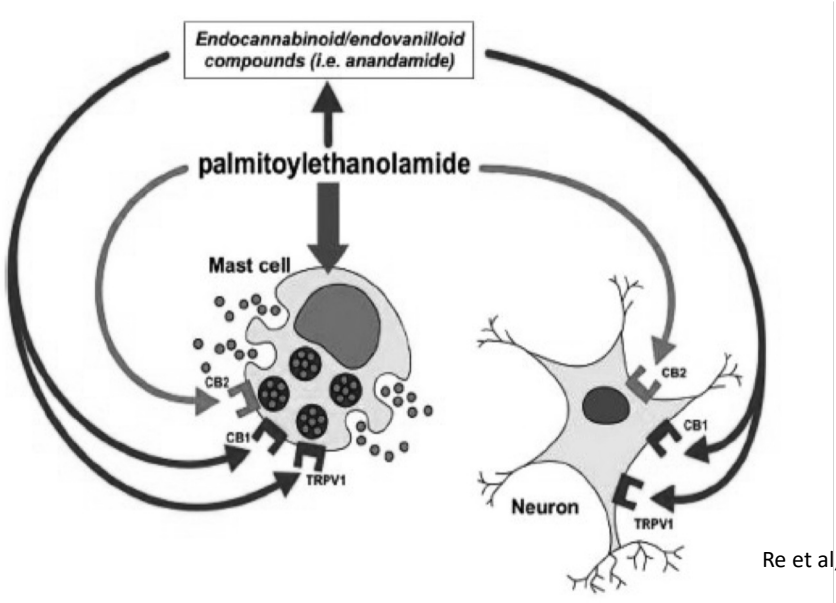
AZIONE DIRETTA E «*EFFETTO ENTURAGE*»



Re et al, 2005

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Possibili ruoli del sistema endocannabinoide

- Controllo del dolore
- Ruolo antiepilettico
- Controllo di nausea e vomito
- Controllo dell'appetito
- Controllo dell'ansia
- Supposto ruolo antitumorale

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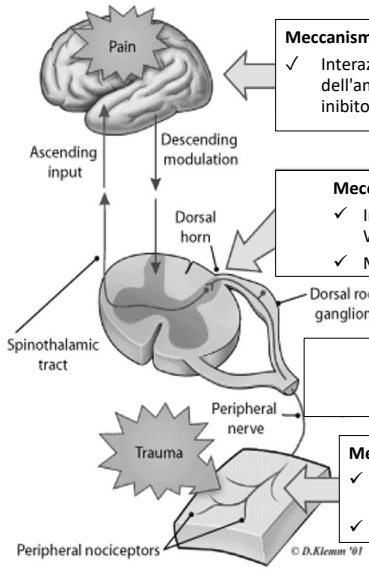
Evidenze supportanti il ruolo degli endocannabinoidi nel **controllo del dolore**



Meccanismi sopraspinali

✓ Interazione con CB1-R a livello di PAG, RVM, alcune aree del talamo e dell'amigdala e del nucleo A5 noradrenergico→ attivazione del controllo inibitorio discendente (oppioidergico e noradrenergico)

Meccanismi spinali

✓ Interazione con CB1-R spinali → < rilascio di glu → < *firing* dei neuroni WDR

✓ Modulazione dell'attività del sistema spinale NA e OPP

Meccanismi periferici

✓ Interazione con CB1-R posti sulle fibre afferenti primarie → < attivazione

✓ Interazione con CB2-R localizzati sulle mast cells → < degranulazione

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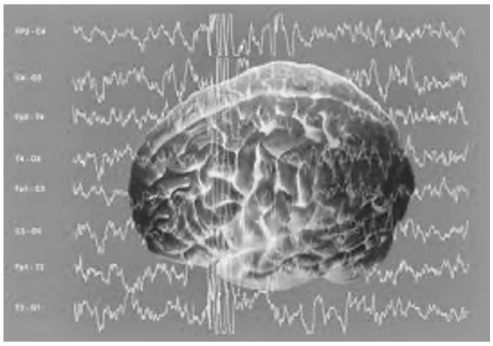
Evidenze supportanti il **ruolo antiepilettico** degli endocannabinoidi

- E' stato dimostrato che il tono endocannabinoide modula lo sviluppo e la durata delle crisi attraverso un rapido **aumento dell'endocannabinoide AEA e l'attivazione del recettore CB1**
  → protezione nei confronti dell'eccitotossicità acuta e dell'attivazione di cascate protettive di segnalazione intracellulare
- Infatti, l'attivazione del recettore CB1:
  - ✓ modula in senso inibitorio tutta una serie di funzioni nervose



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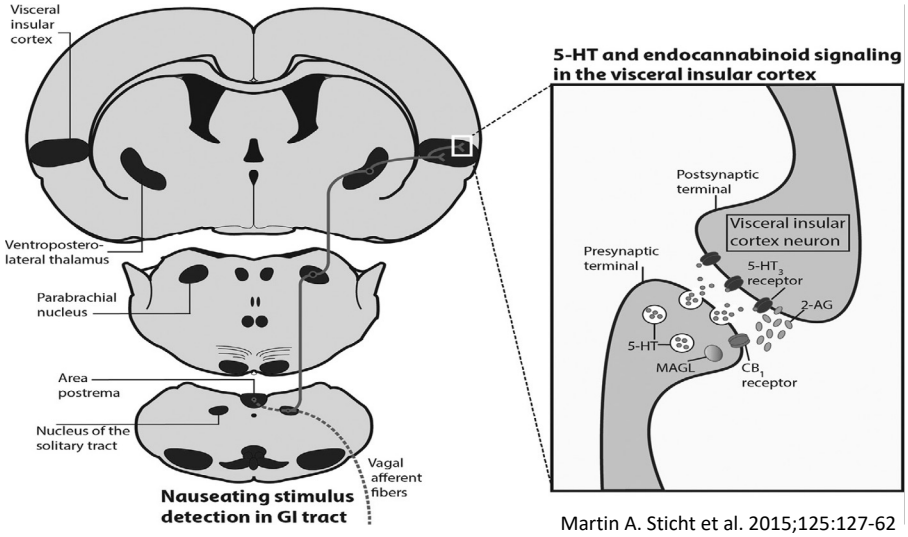
Evidenze supportanti il ruolo degli endocannabinoidi nel **controllo di nausea e vomito**



Martin A. Sticht et al. 2015;125:127-62

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Evidenze supportanti il ruolo degli endocannabinoidi nel **controllo dell'appetito**

- È stato dimostrato che i **cannabinoidi**, quando **iniettati** nell'ipotalamo o nel nucleo accumbens (due aree chiave del cervello per il controllo omeostatico ed edonico dell'assunzione di cibo), stimolano il consumo di cibo **agendo sui recettori CB1**
- Al contrario, il **blocco farmacologico dei recettori CB1** causa effetti anoressizzanti nei roditori esposti a cibo appetibile, anche quando deprivati di alimento per alcune ore, e negli animali obesi

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Evidenze supportanti il ruolo degli endocannabinoidi nel **controllo dell'ansia**

- **Somministrazione di agonisti dei recettori cannabinoidi e di inibitori selettivi della FAAH** → effetti anti-ansia nei roditori
- **Manipolazioni genetiche, che riducono o impediscono l'attivazione del recettore CB1** → ansiogene

Gli effetti del sistema endocannabinoide nella modulazione degli stati ansiosi non sono tuttavia univoci

- La complessità del sistema endocannabinoide è probabilmente responsabile dei diversi effetti, ansiolitici e/o ansiogeni, manifestati da alcune molecole in grado di interagire con i recettori CB1.
- L'azione contradditoria dei recettori CB1 sulle risposte ansiose può infatti essere correlata al ruolo modulatorio conseguente all'attivazione di tali recettori sul rilascio di GABA e di glutammato a livello di amigdala e di altre aree del proencefalo.

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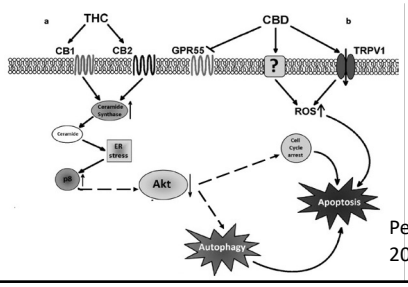
Evidenze supportanti il ruolo **antitumorale** degli endocannabinoidi

- dati riguardanti il ruolo esatto del sistema endocannabinoide nello sviluppo di un tumore sono ancora incoerenti:
  - Riscontro di elevati livelli di endocannabinoidi e sovraespressione dei recettori cannabinoidi in numerose cellule tumorali → eccessiva attivazione del sistema endocannabinoide **pro-tumorigena**?
  - Attivazione dei recettori cannabinoidi è in grado di compromettere lo sviluppo del cancro → ruolo **anti-tumorigeno** della segnalazione endocannabinoide?
- Diversi meccanismi chiamati in causa per spiegare l'azione anti-tumorigena di queste molecole
  - ✓ effetti citotossici o citostatici
  - ✓ induzione dell'apoptosi
  - ✓ inibizione dell'angiogenesi e dell'invasione metastatica del tumore
  - ✓ effetti antinfiammatori



Pellati et al, Biomed Res Int. 2018 4;2018:1691428

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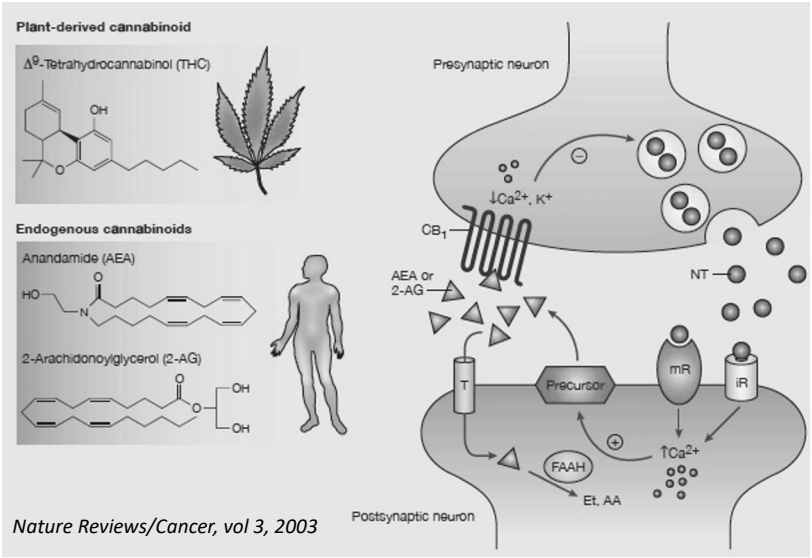
SISTEMA ENDOCANNABINOIDE E CANNABINOIDI ESOGENI



Nature Reviews/Cancer, vol 3, 2003

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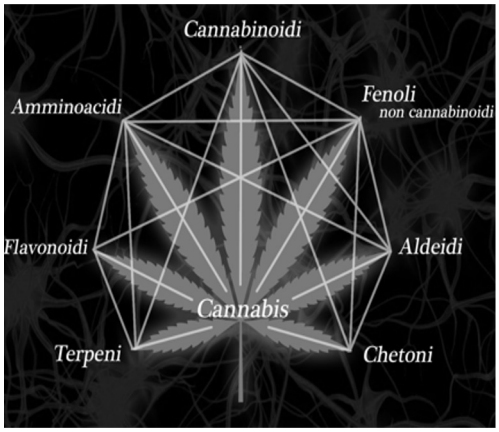
Fitocomplesso della Cannabis



- Fitocannabinoidi
- Terpeni
- Flavonoidi
- Altri componenti

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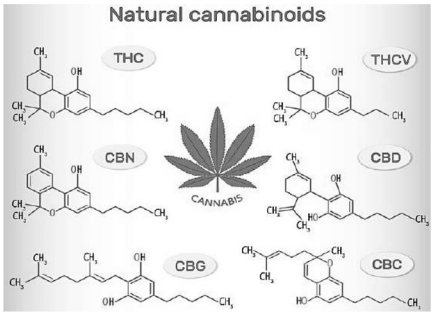
Fitocannabinoidi

- Fitocannabinoidi più rappresentati nella cannabis:
- ***Delta-9-Tetraidrocannabinolo (Δ9-THC)***
- ***Cannabidiolo (CBD)***
- ***Cannabinolo (CBN)***
- ***Cannabigerolo (CBG)***
- ***Cannabicromene (CBC)***
- ***Delta-8-Tetraidrocannabinolo (Δ8-THC)***
- ***Cannabiciclolo (CBL)***
- ***Cannabielsoino (CBE)***
- ***Cannabinidiolo (CBND)***
- ***Cannabitriolo (CBT)***



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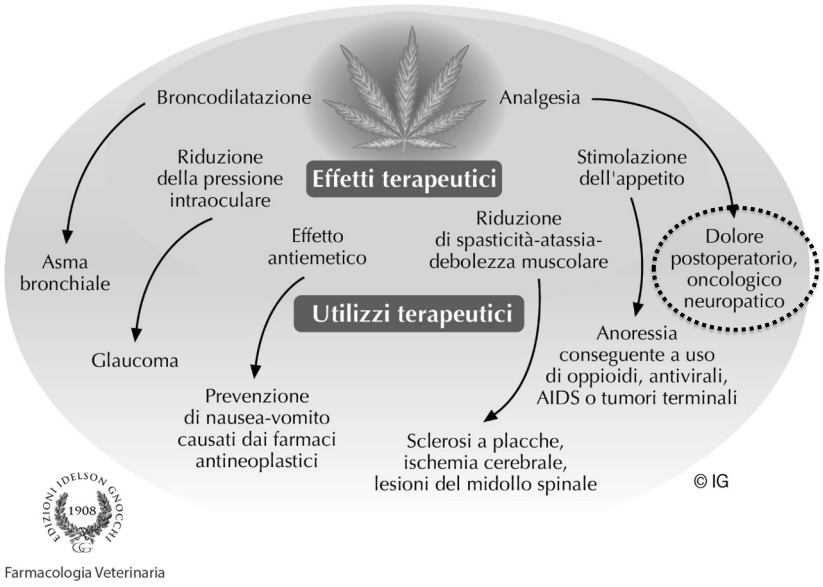
Potenziali impieghi terapeutici



Farmacologia Veterinaria

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Decreto 9/11/2015 (GU 30.11.2015)
Uso medico della cannabis

- ALLEGATO (4.1): «*In considerazione delle evidenze scientifiche fino ad ora prodotte, che dovranno essere aggiornate ogni due anni, si può affermare che* ***l'uso medico della cannabis non può essere considerato una terapia propriamente detta, bensì un trattamento sintomatico di supporto ai trattamenti standard****, quando questi ultimi non hanno prodotto gli effetti desiderati, o hanno provocato effetti secondari non tollerabili, o necessitano di incrementi posologici che potrebbero determinare la comparsa di effetti collaterali.»*

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Decreto 9/11/2015 (GU 30.11.2015)
Uso medico della cannabis

"Gli impieghi di cannabis ad uso medico riguardano:

- ***l'analgesia in patologie che implicano spasticità associata a dolore** (sclerosi multipla, lesioni del midollo spinale) resistente alle terapie convenzionali;*
- ***l'analgesia nel dolore cronico** (con particolare riferimento al dolore neurogeno) in cui il trattamento con antinfiammatori non steroidei o con farmaci cortisonici o oppioidi si sia rivelato inefficace;*
- ***l'effetto anticinetosico ed antiemetico** nella nausea e vomito, causati da chemioterapia, radioterapia, terapie per HIV, che non può essere ottenuto con trattamenti tradizionali;*
- ***l'effetto stimolante dell'appetito** nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici o affetti da AIDS e nell'anoressia nervosa, che non può essere ottenuto con trattamenti standard;*
- ***l'effetto ipotensivo nel glaucoma** resistente alle terapie convenzionali;*
- ***la riduzione dei movimenti involontari del corpo e facciali** nella sindrome di Gilles de la Tourette che non può essere ottenuta con trattamenti standard."*

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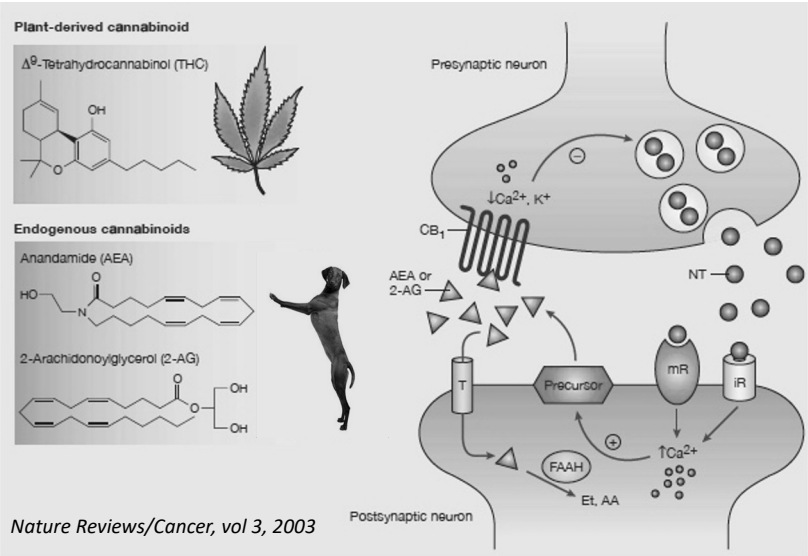
E in medicina veterinaria?



Nature Reviews/Cancer, vol 3, 2003

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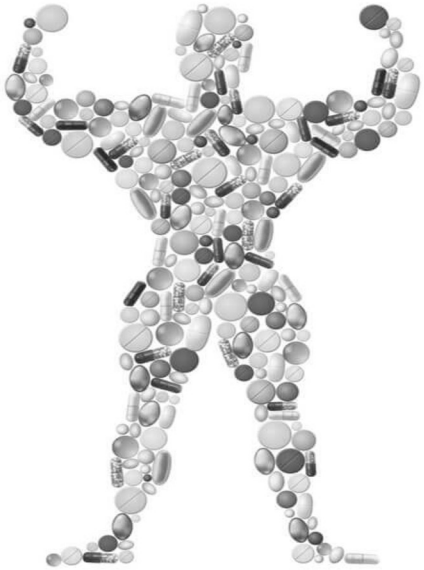
STUDI DI EFFICACIA



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Studi sull'efficacia clinica dei prodotti a base di CBD nel trattamento del **dolore** nel cane

Study design	Dose	Results	Reference
Randomized, placebo-controlled, double-blind, crossover clinical trial to evaluate analgesic efficacy of a CBD-dominant hemp oil (equal mix of CBD and CBDA) on OA-related pain relief in 16 dogs.	2 mg/kg CBD (CBD+CBDA) or placebo orally twice daily for 4 weeks.	CBD produced a significant decrease in pain scores (measured by the Canine Brief Pain Inventory) and an increase in activity levels (measured by the Hudson activity scale).	Gamble et al., 2018
Case report of one dog with chronic osteoarthritis treated with a CBD-purified hemp oil to improve analgesia, mobility, and quality of life.	1 mg/kg of CBD given orally with food twice daily for 30 days.	CBD produced analgesia with consequent improvement of mobility and quality of life of the dog.	De Álava (2019), cited by Coelho et al., 2021
Non-blinded observational study to evaluate the impact of using a CBD-dominant full-spectrum hemp oil-based product as adjunctive therapy on OA-related pain in 32 dogs.	0.3–4.12 mg/kg CBD (individually adjusted dose based on pain assessment) orally twice daily for 90 days.	30 out of 32 dogs showed pain relief (measured using a 0 to10 scale, with 10 representing the worst possible pain) and 21 out of 23 dogs were able to reduce or stop gabapentin after adding the CBD-dominant oil.	Kogan et al., 2020
Randomized, placebo-controlled, double-blind clinical trial to evaluate the safety and therapeutic potential of different doses and formulations of hemp-derived CBD oil for OA pain relief in 20 dogs.	20 mg/day of naked CBD, 50 mg/day of naked CBD, 20 mg/day of liposomal CBD or placebo orally for 4 weeks.	CBD significantly reduced pain (measured by the Helsinki Chronic Pain Index) and increased mobility in a dose-dependent manner. Liposomal CBD (20 mg/day) was as effective as the highest dose of non-liposomal CBD (50 mg/day) in improving clinical outcomes.	Verrico et al., 2020
Randomized placebo-controlled study to evaluate the efficacy of a pure CBD oil formulation, included in a multimodal drug regimen, in relieving pain in 9 dogs with spontaneous OA.	2 mg/kg of CBD administered orally transmucosally (OTM) twice daily for 12 weeks, added to the multimodal drug protocol.	Adding oral OTM CBD to a multimodal pharmacological treatment for canine OA improved owner-reported pain scores and quality of life of dogs (measured by the Canine Brief Pain Inventory).	Brioschi et al, 2020
Double-blind, randomized, placebo-controlled, cross-over clinical study to evaluate the efficacy of a CBD-dominant hemp oil on OA-related pain relief in 23 dogs.	2.5 mg/kg of CBD orally twice daily for 6 weeks.	No differences were observed between groups at any time point for any of the recorded outcome measures (objective gait analysis, activity counts - via accelerometry - and clinical metrology instruments - Liverpool Osteoarthritis in Dogs and Canine Brief Pain Inventory).	Mejia et al., 2021
Randomized, placebo controlled, blinded clinical trial to determine the impact of capsules containing a CBD/CBDA rich hemp oil on acute post-operative pain in dogs following a tibial plateau levelling osteotomy (TPLO).	2–2.5mg/kg of CBD/CBDA orally twice daily for 4 weeks following a TPLO.	No significant differences were noted between placebo and CBD/CBDA groups at any point in Canine Brief Pain Inventory scores, degree of lameness, and degree of weight-bearing.	Klatzkow et al., 2023

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frontiers | Frontiers in Veterinary Science

TYPE Original Research
PUBLISHED 23 August 2023
DOI 10.3389/fvets.2023.1224452

Therapeutic efficacy and pharmacokinetics of liposomal-cannabidiol injection: a pilot clinical study in dogs with naturally-occurring osteoarthritis

Conclusion: Liposomal-CBD administered subcutaneously produced detectable CBD plasma concentrations for 6 weeks with minimal side effects and demonstrated reduced pain and increased wellbeing as part of multimodal pain management in dogs suffering from osteoarthritis. Further placebo-controlled studies are of interest.

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animals

Animals **2023**, *13*, 2716. https://doi.org/10.3390/ani13172716 MDPI

Article

Placebo-Controlled Trial of Daily Oral Cannabidiol as Adjunctive Treatment for Cats with Chronic Gingivostomatitis

Abstract: A placebo-controlled study evaluated the clinical efficacy and safety of a commercially available cannabidiol (CBD) oral formulation as an adjunctive treatment for pain management for feline chronic gingivostomatitis (FCGS). CBD was included in a multimodal treatment routinely performed on client-owned cats with FCGS that were submitted to dental extractions. Twenty-two cats were consecutively included in the study. The first group was treated using a fixed dosage of 4 mg per cat every 12 h for 15 consecutive days, and the second received a placebo of similar features. Treatments began 2 h before dental extractions. Pain and disease severity were assessed at days 0 and 15 using the Composite Oral Pain Scale (COPS-C/F) and the Stomatitis Disease Activity Index score (SDAI). Weight, vital and biochemistry parameters, and analgesic reinforcement needs were also registered at the same time points. In the treated cats, blood was collected after 4, 8, and 12 h to determine CBD serum concentrations using ultra-high-performance liquid chromatography–mass spectrometry (UHPLC-MS/MS). After data analysis using mixed models, a significant improvement in the SDAI scores of cats medicated with CBD was found. The protocol is safe since severe adverse effects and biochemical changes were not observed during the treatment period. This study suggests that the cats benefited from this treatment.

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Studi sull'efficacia clinica dei prodotti a base di CBD nel trattamento dell'**epilessia** nel cane

Study design	Dose	Results	Reference
Randomized placebo-controlled, double-blinded clinical trial to assess the effect of using a CBD-infused hemp oil in addition to conventional antiepileptic treatment on seizure frequency in 26 dogs with idiopathic epilepsy.	2.5 mg/kg of CBD or placebo oil orally twice daily for 12 weeks.	Compared with the placebo group, dogs in the CBD group had a significant reduction in seizure frequency (median change, 33%). However, the proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups.	McGrath et al., 2019
Case report of three dogs with suspected epilepsy, each one treated with a different dose of a CBD-predominant full-spectrum hemp oil.	0.51 mg/kg of CBD for the first dog, 1.24–1.25 mg/kg for the second dog, and 5 mg/kg for the third dog, given orally twice daily for 8 weeks.	Considerable reduction in epileptic seizures frequency and improvement of other signs (i.e., undesirable behavior) in one dog, slight improvement of seizure intensity in another, and no response to therapy in the third, as reported by the owners.	Mogi and Fukuyama, 2019
Randomized, controlled-placebo, cross-over study to examine the efficacy of a CBD and CBDA-rich hemp product for the treatment of refractory epileptic seizures in 14 dogs.	2 mg/kg of CBD orally twice daily for 12-week.	Statistically significant reduction in epileptic seizure frequency, as well as number of epileptic seizure days (the number of dogs with a 50% reduction in epileptic activity while on treatment were 6/14, whereas 0/14 had reductions of 50% or greater while on the placebo).	Garcia et al., 2023

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Studies on clinical efficacy of CBD-based products in the treatment of **skin diseases** in dogs

Study design	Dose	Results	Reference
Retrospective study to examine the effect of a 10% CBD-containing broad-spectrum hemp oil as a supplemental treatment for canine atopic dermatitis in 8 dogs.	Initial dose: 0.07 to 0.25 mg/kg of CBD orally twice daily. The dose was increased depending on the skin condition of each dog and the observed response at 0.125 mg/kg. Administration for at list 8 weeks.	CBD decreased the occurrence of pruritus in dogs with canine atopic dermatitis.	Mogi et al 2022
Randomised, double-blinded and placebo-controlled trial to determine if CBD/CBDA-rich hemp extract (in gelatin capsules) decreased pruritus and cutaneous lesions in 17 dogs with atopic dermatitis.	2 mg/kg of CBD/CBDA twice daily orally for 28 days.	CBD/CBDA does not affect lesion severity yet does have a positive effect on pruritus as an adjunct therapy in some dogs with atopic dermatitis.	Loewinger et al., 2022
Randomized complete block design, placebo controlled, to determine the influence of CBD treats on the daily activity in adult dogs.	2.5 mg/kg (LOW) and or 5.0 mg/kg (HIGH) of CBD per day (split in 2 administrations) orally for 7 days before and another 14-day during collection of activity.	CBD (LOW and HIGH) did not alter the total daily activity points or activity duration but tended (P = 0.071) to reduce total daily scratching compared with the control.	Morris et al., 2021

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Studi sull'efficacia clinica dei prodotti a base di CBD nel trattamento di **disordini comportamentali** nel cane

Study design	Dose	Results	Reference
Replicated 4X4 Latin square design experiment to evaluate the influence of a CBD industrial hemp extract incorporated into treats on behavioral responses to fear-inducing stimuli in 16 dogs.	1.4 mg/kg of CBD orally 4-6 h prior the test.	The results of the current study did not provide strong support of an anxiolytic effect of CBD in dogs.	Morris et al., 2020
Placebo controlled study design to determine if a 5% CBD based oil affects stress related behaviour in 12 shelter dogs.	1 drop of oil/2 kg (~1.25 mg/kg) of CBD orally once a day for 45 days.	Aggressive behaviour towards humans decreased significantly over time in CBD treatment group. However, in the pairwise comparisons, only the T0-T2 (45th day) comparison was significant.	Corsetti et al., 2021
Blinded, placebo-controlled, parallel design study to determine the anxiolytic effect of a CBD based hemp derived distillate incorporated into soft gel capsules in dogs experiencing a separation event (n.=21) or a car travel (n.=19).	~ 4 mg/kg of CBD orally 2 h prior the test.	The mitigating effect of CBD treatment varied by outcome measures and tests, with some indicating a significant reduction in canine stress compared to the placebo group.	Hunt et al 2023

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EVIDENZE EMPIRICHE

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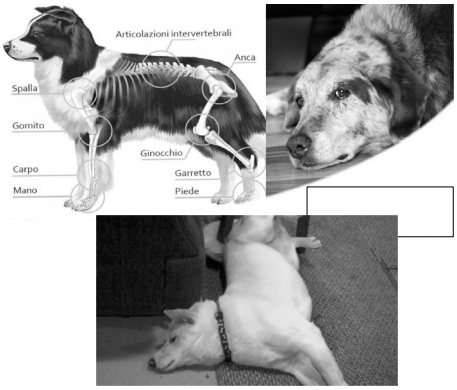
Evidenze empiriche

- Dolore da osteoartrosi (cane e gatto)
- Dolore oncologico
- Sindrome da iperestesia felina
- Epilessia
- Ansia e insonnia
- …

→EFFICACIA

→TOLLERABILTA'



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GRAZIE PER L'ATTENZIONE

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