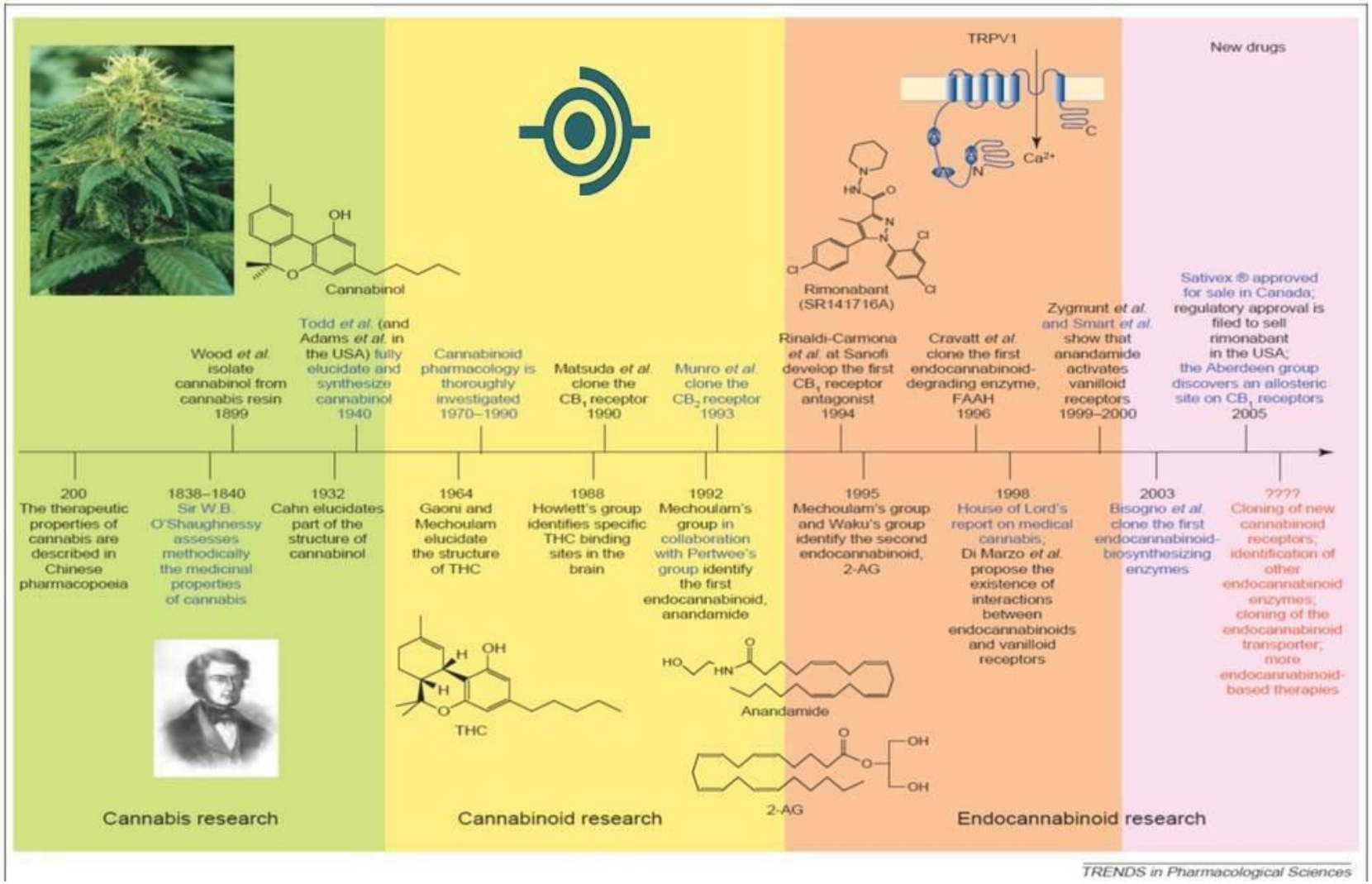
Cannabinoidi, una nuova frontiera nella terapia antalgica e nelle cure palliative?

Dr. Felice Spaccavento
Anestesista Rianimatore
Coordinatore UOC Cure Palliative ASL BA

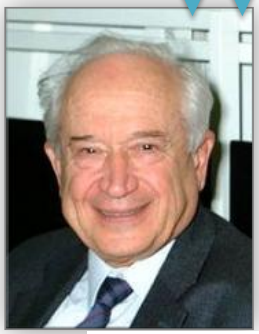
XIX CONGRESSO NAZIONALE CARD

Nelle steppe siberiane è stato rinvenuto un tumulo funerario del 500 a.C. di una giovane donna morta di tumore mammario.

Tomba del III sec. In Cina ritrovato un corpo di ragazza morta durante il parto.


TRPV1
New drugs
Cannabinol
Rimonabant (SR141716A)
200 The therapeutic properties of cannabis are described in Chinese pharmacopoeia
1838–1840 Sir W.B. O'Shaughnessy assesses methodically the medicinal properties of cannabis
Wood et al. isolate cannabinol from cannabis resin 1899
1932 Cahn elucidates part of the structure of cannabinol
Todd et al. (and Adams et al. in the USA) fully elucidate and synthesize cannabinol 1940
1964 Gaoni and Mechoulam elucidate the structure of THC
Cannabinoid pharmacology is thoroughly investigated 1970–1990
1988 Howlett's group identifies specific THC binding sites in the brain
Matsuda et al. clone the CB1 receptor 1990
1992 Mechoulam's group in collaboration with Pertwee's group identify the first endocannabinoid, anandamide
Munro et al. clone the CB2 receptor 1993
1995 Mechoulam's group and Waku's group identify the second endocannabinoid, 2-AG
Rinaldi-Carmona et al. at Sanofi develop the first CB1 receptor antagonist 1994
1998 House of Lord's report on medical cannabis; Di Marzo et al. propose the existence of interactions between endocannabinoids and vanilloid receptors
Cravatt et al. clone the first endocannabinoid-degrading enzyme, FAAH 1996
Zygmunt et al. and Smart et al. show that anandamide activates vanilloid receptors 1999–2000
2003 Bisogno et al. clone the first endocannabinoid-biosynthesizing enzymes
Sativex ® approved for sale in Canada; regulatory approval is filed to sell rimonabant in the USA; the Aberdeen group discovers an allosteric site on CB1 receptors 2005
???? Cloning of new cannabinoid receptors; identification of other endocannabinoid enzymes; cloning of the endocannabinoid transporter; more endocannabinoid-based therapies
THC
Anandamide
2-AG
Cannabis research
Cannabinoid research
Endocannabinoid research
TRENDS in Pharmacological Sciences

1964: Isolamento THC
1988: Scoperta dei recettori CB_1
1990: Recettori clonati e sequenziati
1992: Scoperta degli endocannabinoidi
1993: Scoperta del secondo recettore(CB_2)
1994: Sviluppato il primo antagonista CB_1
1997: Sviluppato il primo antagonista CB_1
2000: Identificazione dell'enzima FAAH
2000: Disponibili topi knock-out CB_1
2001: Disponibili topi knock-out CB_2



Raphael Mechoulam
Professor of Medicinal Chemistry and Natural Products at the Hebrew University of Jerusalem

I recettori dei cannabinoidi sono stati scoperti in tutti gli animali, anche al più basso livello evolutivo, come gli invertebrati marini

Endocannabinoidi

- **Anandamide**
- **2-AG (*Arachidoglicerolo*)**
- **Metaboliti lipidici (PEA)**

Recettori

eCB1 (SNC)

eCB2 (Immunomodulante)

TRPV1

PPAR's

GPR55

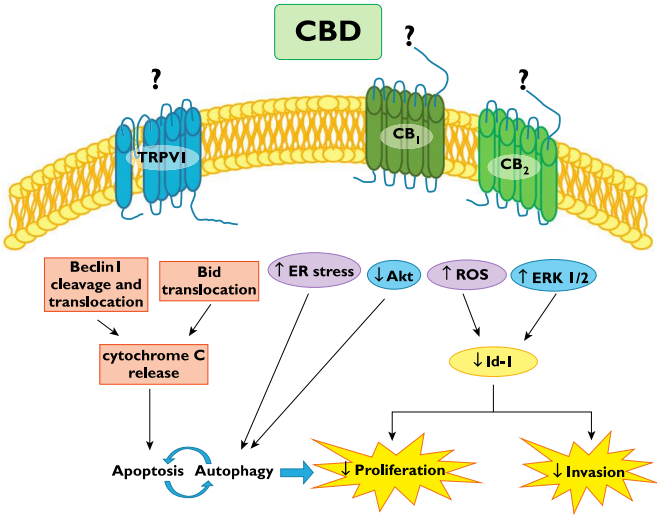
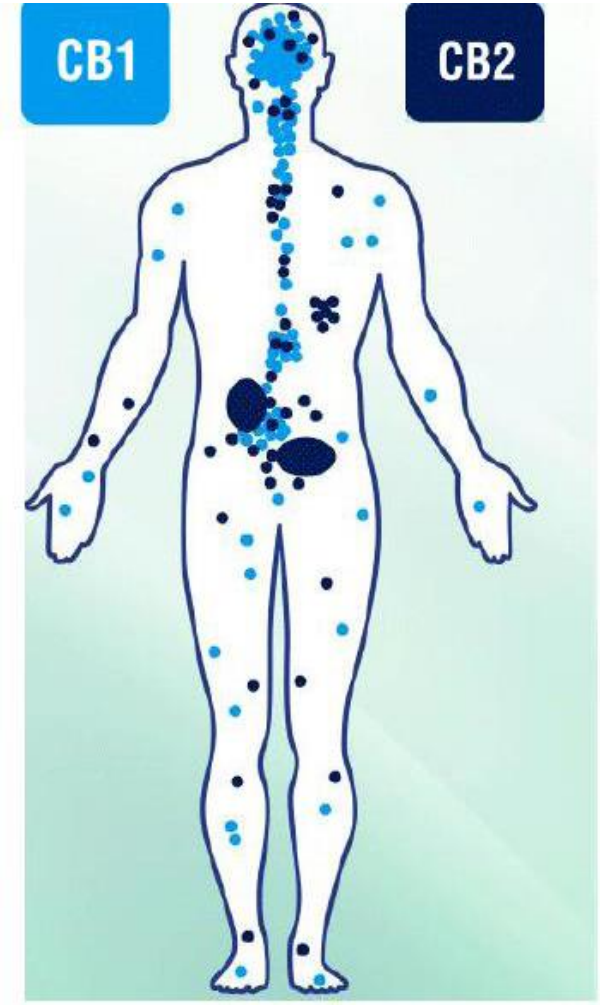
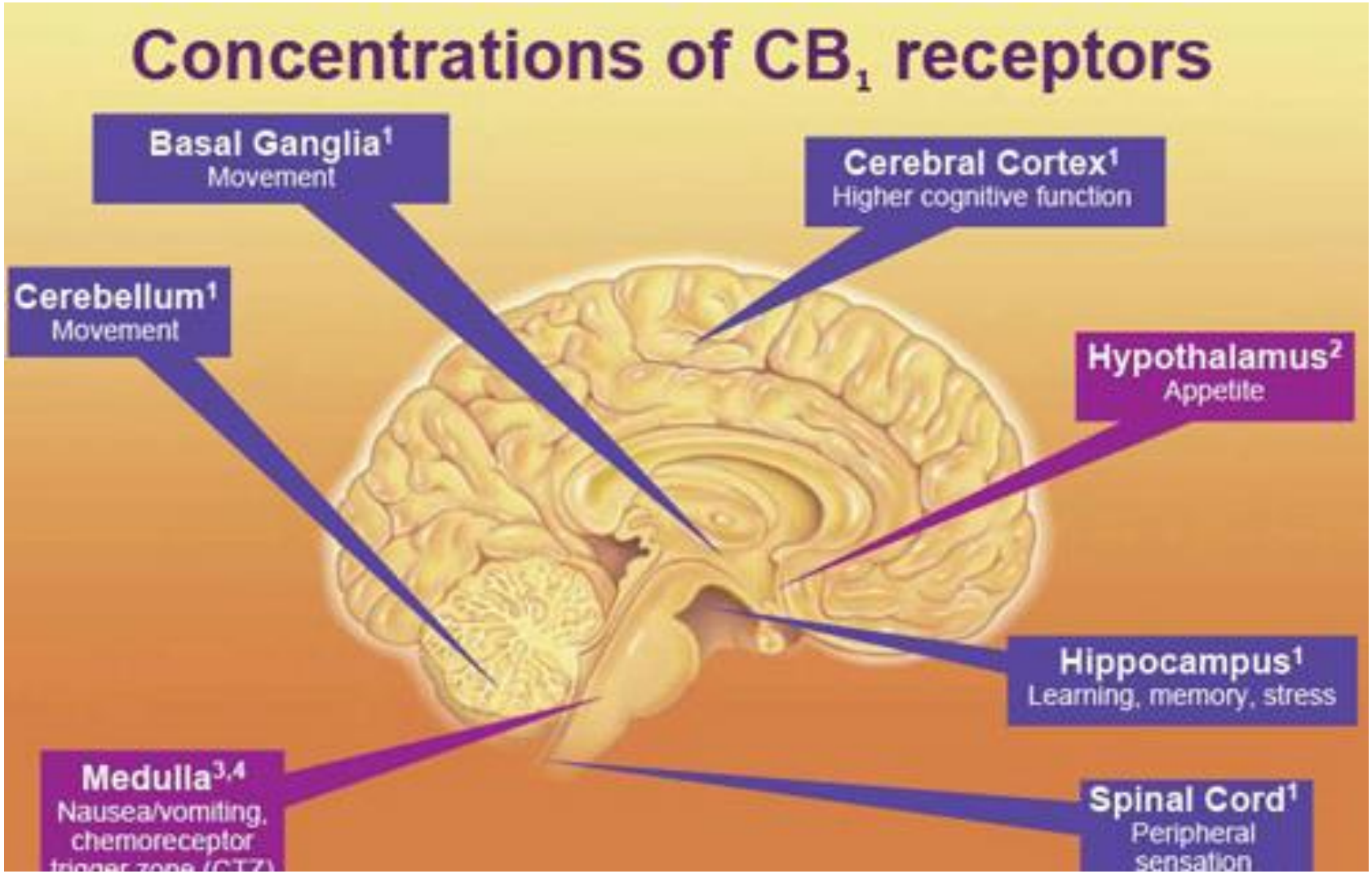
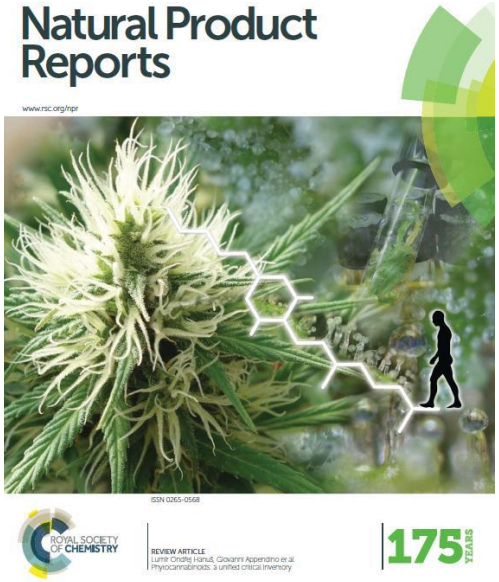


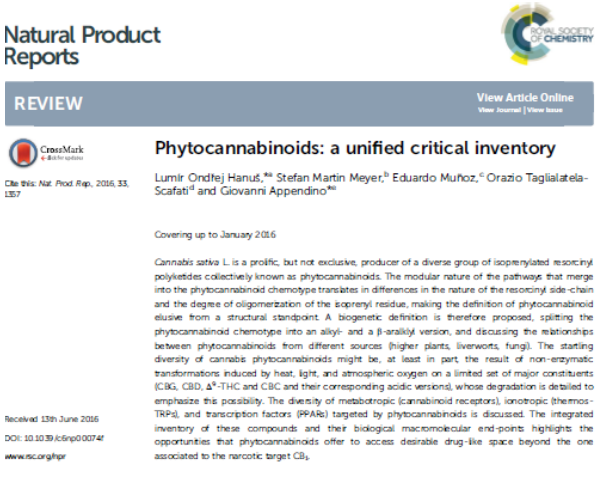
Figure 3
Schematic representation of the signalling pathways associated with CBD effects on breast cancer

Sede dei recettori




Concentrations of CB1 receptors
Basal Ganglia1
Movement
Cerebral Cortex1
Higher cognitive function
Cerebellum1
Movement
Hypothalamus2
Appetite
Hippocampus1
Learning, memory, stress
Medulla3,4
Nausea/vomiting,
chemoreceptor
Spinal Cord1
Peripheral
sensation





Natural Product Reports

REVIEW

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Phytocannabinoids: a unified critical inventory

Lumír Ondřej Hanuš,[a*] Stefan Martin Meyer,[b] Eduardo Muñoz,[c] Orazio Taglialatela-Scafati[d] and Giovanni Appendino[e*]

Covering up to January 2016

Cannabis sativa L. is a prolific, but not exclusive, producer of a diverse group of isoprenylated resorcinyl polyketides collectively known as phytocannabinoids. The modular nature of the pathways that merge into the phytocannabinoid chemotype translates in differences in the nature of the resorcinyl side-chain and the degree of oligomerization of the isoprenyl residue, making the definition of phytocannabinoid elusive from a structural standpoint. A biogenetic definition is therefore proposed, splitting the phytocannabinoid chemotype into an alkyl- and a (l-aralkyl version, and discussing the relationships between phytocannabinoids from different sources (higher plants, liverworts, fungi). The startling diversity of cannabis phytocannabinoids might be, at least in part, the result of non-enzymatic transformations induced by heat, light, and atmospheric oxygen on a limited set of major constituents (CBG, CBD, Δ^9-THC and CBC and their corresponding acidic versions), whose degradation is detailed to emphasize this possibility. The diversity of metabotropic (cannabinoid receptors), ionotropic (thermos-TRPs), and transcription factors (PPARs) targeted by phytocannabinoids is discussed. The integrated inventory of these compounds and their biological macromolecular end-points highlights the opportunities that phytocannabinoids offer to access desirable drug-like space beyond the one associated to the narcotic target CB_1.

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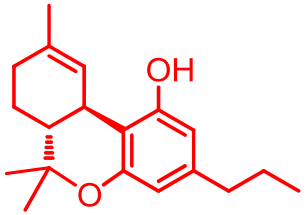
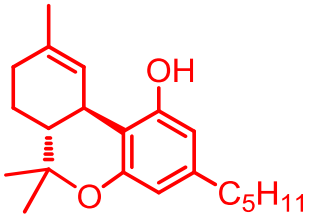
www.rsc.org/npr

CBC

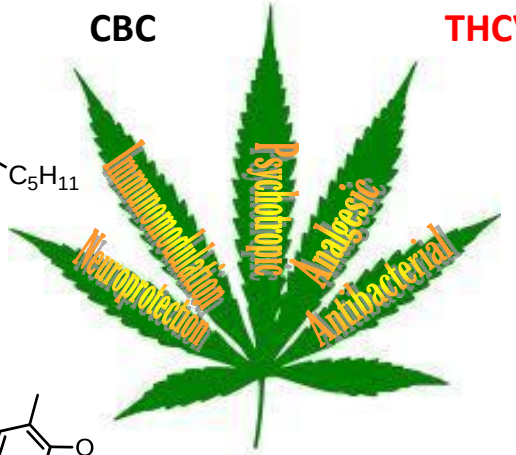


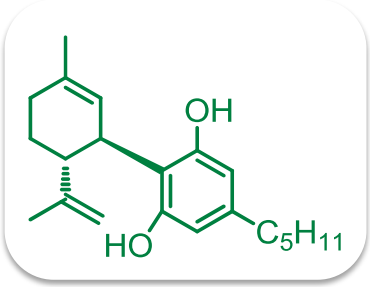
THCV



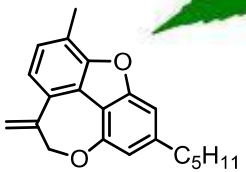
THC

CBG

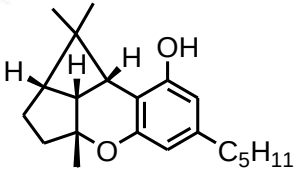




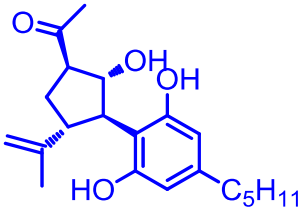
CBD



CBX



CBL

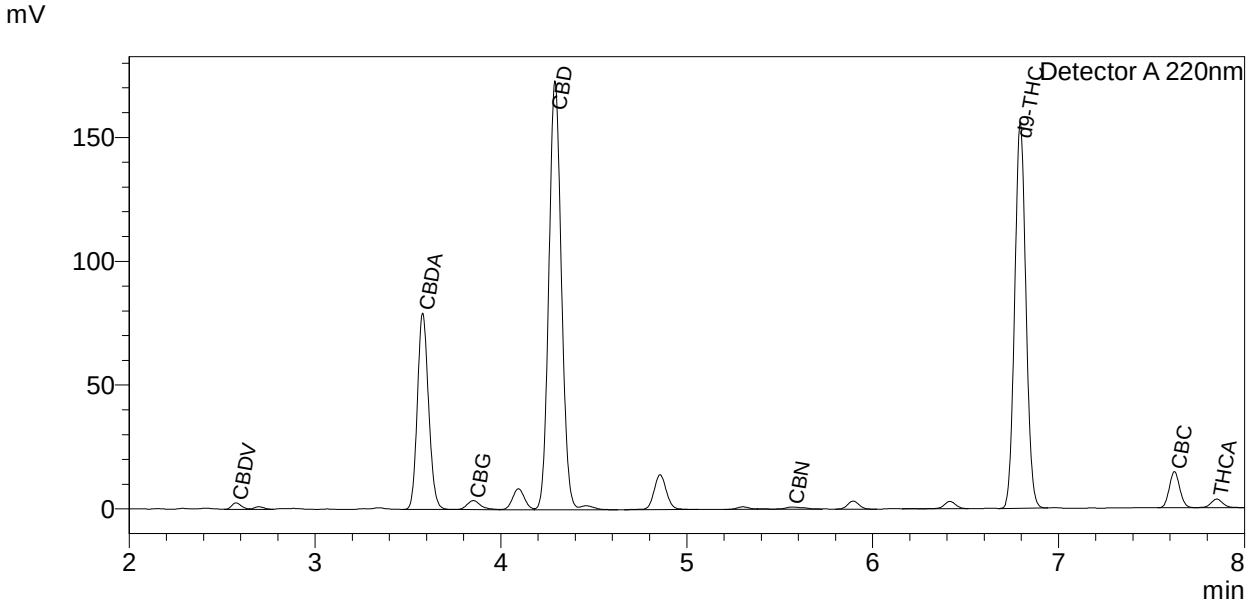


CBM

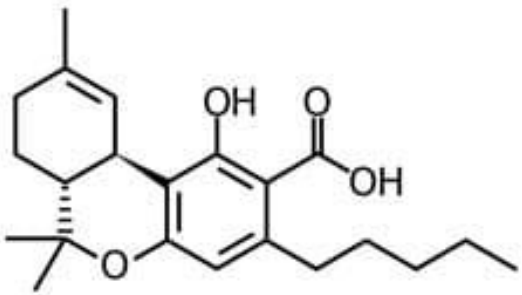
Informazioni sul campione

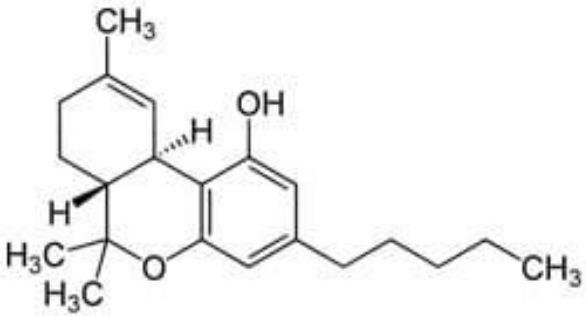
Data Filename : fm220211014.lcd
Method Filename : HighSensitivity_FORMULA.lcm
Injection Volume : 5 uL
Sample Amount : 0,99 mg
Date Acquired : 14/10/2021 11:37:23

Cromatogramma



DECARBOXYLATION REACTION





THCA $\xrightarrow{> 110^\circ}$ THC

Range: 140° - 257° f **120° C**	Tetrahydrocannabinol THCA	Anorexia, Nausea, Chemotherapy, pain relief	Link to Wiki: https://en.wikipedia.org/wiki/Tetrahydrocannabinolic_acid
Range: 176° - 275° f **130° C**	Cannabidiol CBDA	Inflammation, Arthritis, Chemotherapy	https://en.wikipedia.org/wiki/Cannabidiol#Pharmacodynamics
Range: 212° - 293° f **140° C**	Cannabichromene CBCA	Inflammation, Antiviral, Analgesic/Pain Killer	https://en.wikipedia.org/wiki/Cannabichromene
Boil Point 315° f **155° C**	Tetrahydrocannabinol THC	Anorexia, Cachexia, Gastrointestinal Disorders, Nausea, Crohn's, Stress, Multiple Sclerosis,	https://en.wikipedia.org/wiki/Tetrahydrocannabinol
Range: 320° - 356° f **165° C**	Cannabidiol CBD	Pain Killer, Insomnia, Arthritis, Gastrointestinal, Nausea, Crohn's, Anxiety, Stress, Bipolar, Depression, Chemotherapy	https://en.wikipedia.org/wiki/Cannabidiol
Boil Point 351° f **175° C**	Tetrahydrocannabinol THC	Alzheimer's, Parkinson's, Spasticity, ALS, Asthma, Fatigue, Hypertension, Glaucoma, HIV/AIDS, Sleep Apnea, Pain Killer	https://en.wikipedia.org/wiki/Tetrahydrocannabinol
Boil Point 365° f **185° C**	Cannabinol CBN	Epilepsy, Multiple Sclerosis, Spasticity, ALS, Fibromyalgia, Insomnia, Pain Killer, Arthritis, Inflammation, Depression	https://en.wikipedia.org/wiki/Cannabinol
Boil Point Theory **195° C**	Cannabielsoin CBE	Sedative, Antidepressant, Anxiolytic, Immunostimulators	https://de.wikipedia.org/wiki/Cannabielsoin
High Benzene Level **205° C**	*Hydrocarbons* Benzene	Toxic/Harmful Vapors at 392° f	https://en.wikipedia.org/wiki/Aromatic_hydrocarbon

TERPENI

I terpeni sono oli essenziali che si presentano naturalmente e conferiscono agli aromi e ai sapori distintivi della pianta di cannabis. La sua ricerca ha rivelato che i terpeni potrebbero produrre una sinergia in relazione al trattamento del dolore, dell'infiammazione, della depressione, dell'ansia, della dipendenza, dell'epilessia, del cancro, delle infezioni fungine e batteriche".

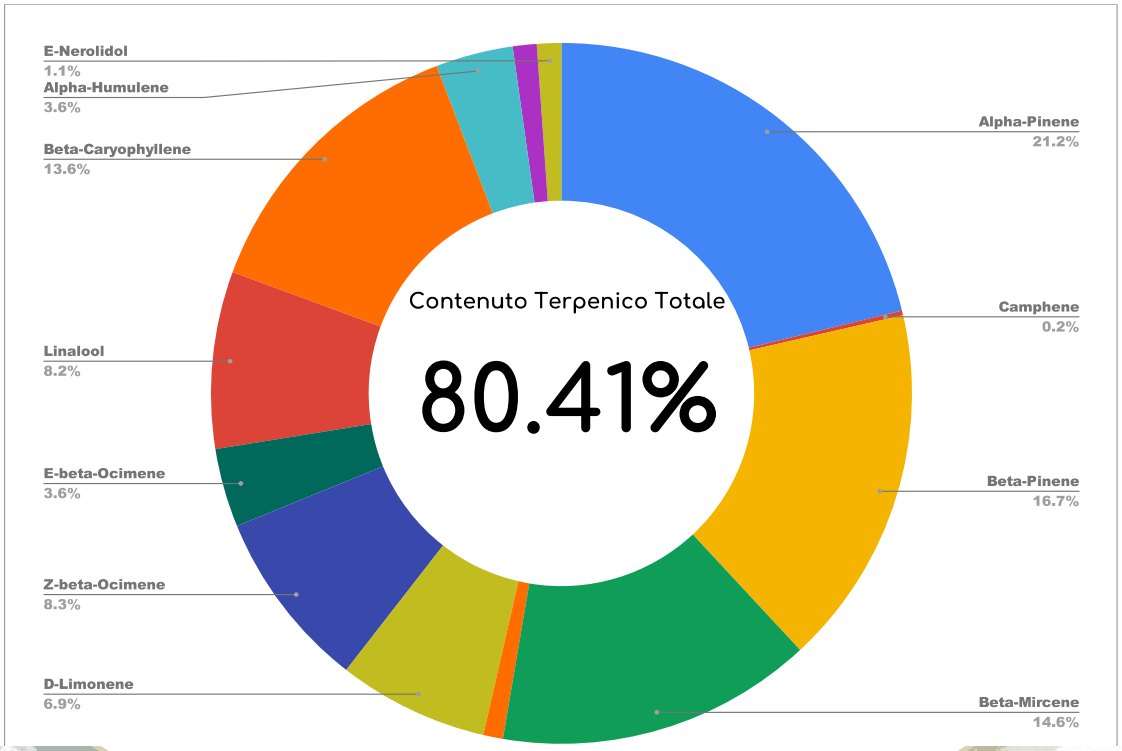
- Il **limonene** è un terpene energizzante in grado di alleviare i sintomi della **depressione**.
- Il **Beta-Caryophyllene** è potente nel ridurre l'**infiammazione** in tutto il corpo, compreso il sistema gastrointestinale.
- Il **mircene** ha effetti **sedativi** che promuovono la calma e forniscono sollievo dall'ansia.
- **Linalool** è anche un **anti-ansia** e in grado di agire come un **anti-microbico**.
- **Pinene** combatte **i problemi cognitivi** e di memoria aumentando la concentrazione.

TERP - Profilo Terpenico

Analita	Risultato mg/g	Quantità relativa %
Alpha-Pinene	170.484	21.20
Camphene	1.734	0.22
Beta-Pinene	133.967	16.66
Beta-Myrcene	117.378	14.60
Delta-3-Carene	7.304	0.91
Alpha-Terpinen	0.000	0.00
p-Cymene	0.000	0.00
D-Limonene	55.780	6.94
Z-beta-Ocimene	66.761	8.30
Eucalyptol	0.000	0.00
E-beta-Ocimene	29.243	3.64
Gamma-Terpinene	0.000	0.00

Analita	Risultato mg/g	Quantità relativa %
Terpinolen	0.000	0.00
Linalool	65.700	8.17
Isopulegol	0.000	0.00
Geraniol	0.000	0.00
Beta-Caryophyllene	109.185	13.58
Alpha-Humulene	28.707	3.57
Z-Nerolidol	8.846	1.10
E-Nerolidol	9.045	1.12
Caryophyllene oxide	0.000	0.00
Guaiol	0.000	0.00
Alpha-Bisabolol	0.000	0.00
Contenuto Terpenico Totale	**804.13 mg/g**	**80.41%**

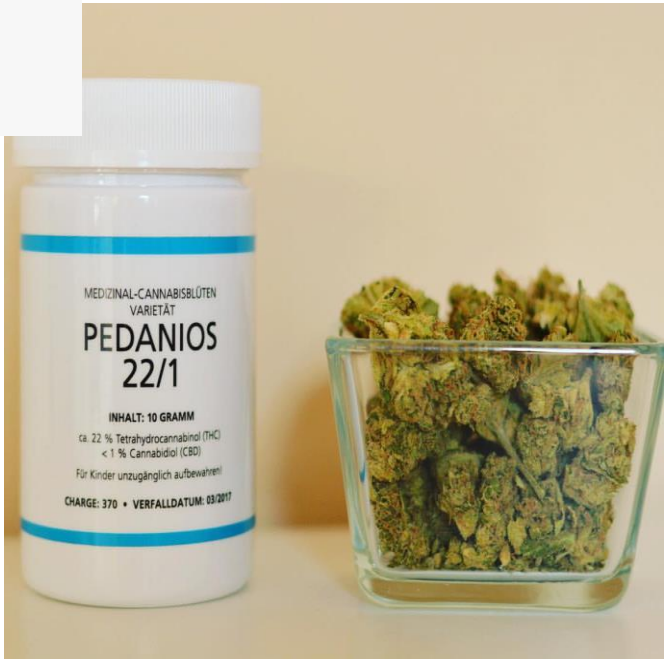
Rappresentazione grafica del profilo Terpenico



The
ENTOURAGE
EFFECT
CBG
CBD
THCa
CBC
CBDa
THC
CBN
THCv

CANNABIS FLOS
Bedrocan
5 gram

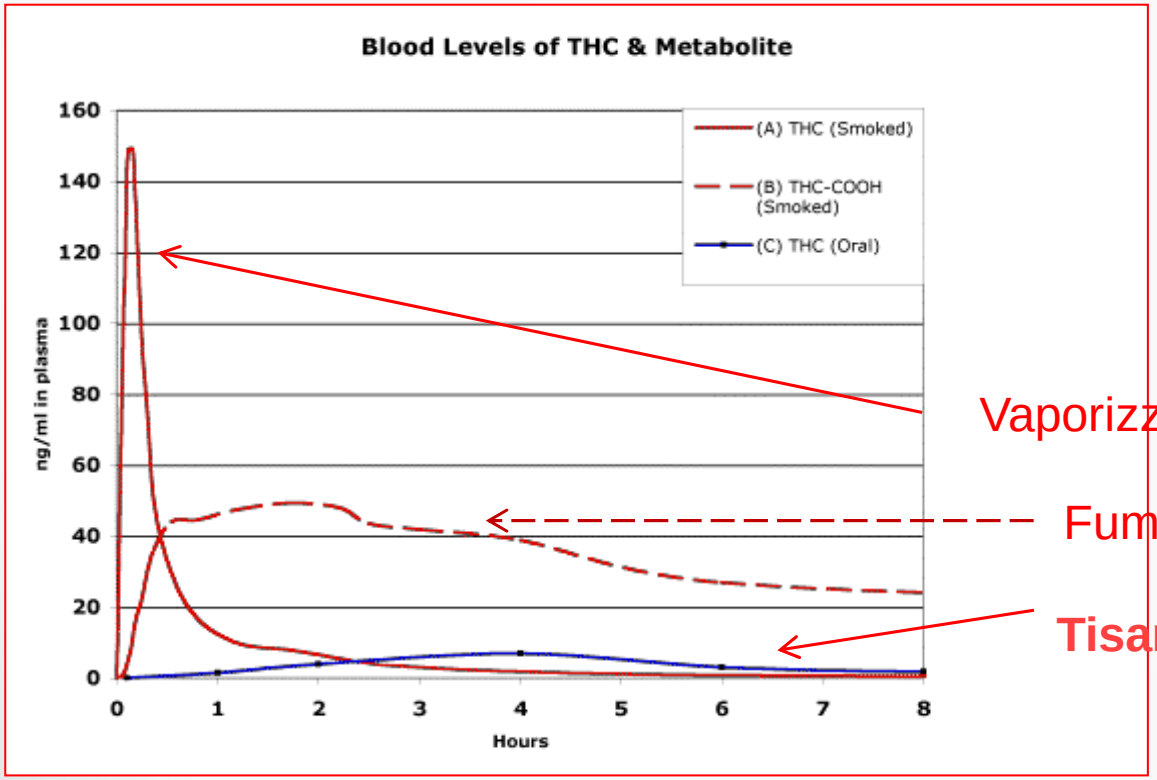
CANNABIS FM2
g
INCOMPLETO


MEDIZINAL-CANNABISBLÜTEN
VARIETÄT
PEDANIOS
22/1
INHALT: 10 GRAMM
ca. 22 % Tetrahydrocannabinol (THC)
< 1 % Cannabidiol (CBD)
Für Kinder unzugänglich aufbewahren!
CHARGE: 370 • VERFALLDATUM: 03/2017

In base a questa, il Medico che volesse prescrivere una varietà di cannabis con il

Cannabis Medica	Varietà	Olandese	Italiana	Canadese
22% THC <1% CBD	SATIVA	Bedrocan	–	Pedanios
14% THC <1% CBD	**INDICA**	**Bedica**	–	–
12% THC <1% CBD	SATIVA	Bedrobinol	–	–
7.5-8% THC 8-12% CBD	SATIVA	Bediol	FM2	Pedanios (INDICA)
< 1% THC 9% CBD	SATIVA	Bedrolite	–	Pedanios (HYBRID)

	I primi effetti	Effetto massimo	Durata massima
Inalazione	5 min	15 min	3-4 ore
Orale	30-90 min	2-3ore	4-8 ore



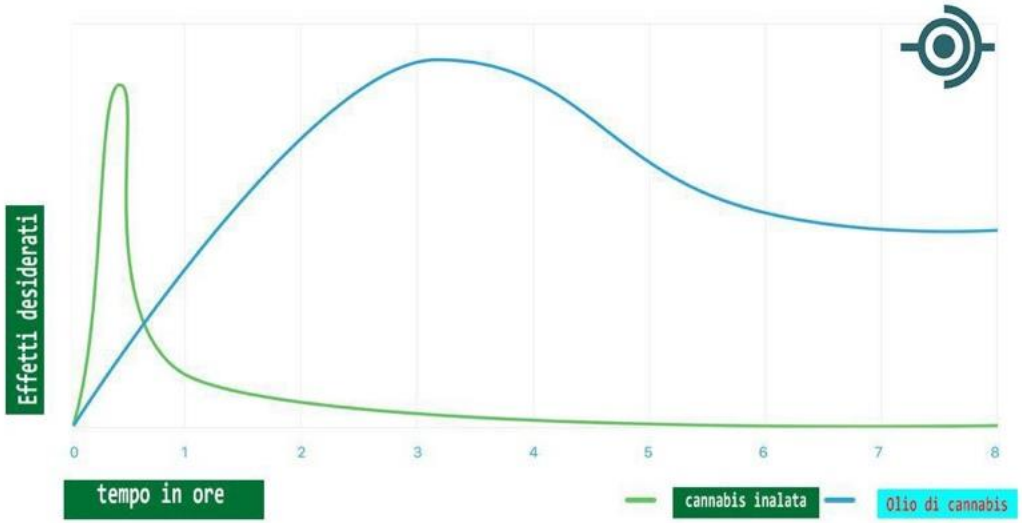
Vaporizzata

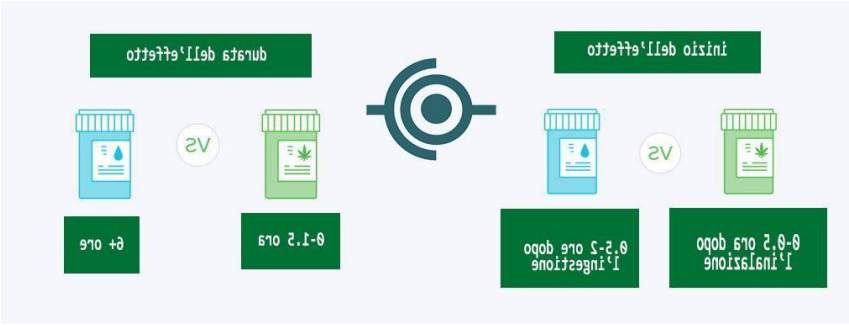
Fumata

Tisana

Assorbimento della Cannabis

In confronto alla cannabis inalata, l'olio di cannabis ingerito viene elaborato in modo diverso nel corpo. Ciò si traduce in un graduale inizio di effetti che durano più a lungo nel corpo.





Metabolismo

- **I cannabinoidi subiscono metabolismo epatico ad opera degli enzimi citocromiali P450.**

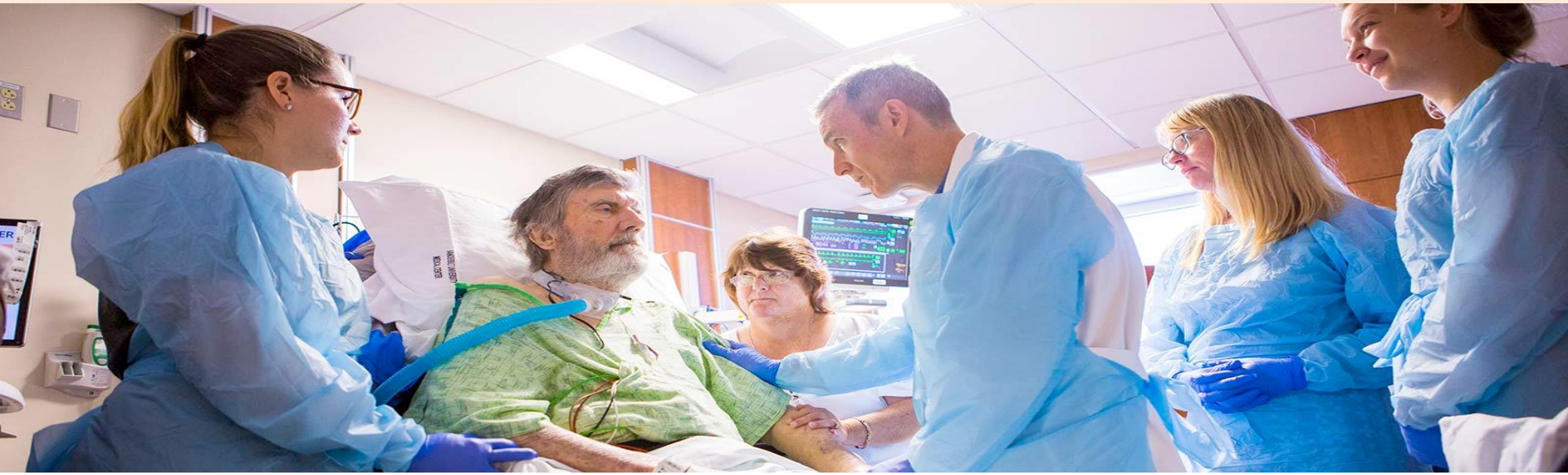
- Il delta-9-tetraidrocannabinolo (THC), è convertito a 11-idrossi-tetraidrocannabinolo (11-OH-THC), farmacologicamente attivo ed equipotente al tetraidrocannabinolo, poi a 11-nor-9-carbossi-delta-9-tetraidrocannabinolo (THC-COOH), inattivo, che rappresenta il metabolita maggiormente presente nel sangue e nelle urine (Huestis, Cone, 1998). La conversione del THC a 11-OH-THC è catalizzata dall'enzima citocromiale CYP2C9. Sono stati identificati anche altri metaboliti idrossilati, di minor importanza, ottenuti per azione del CYP3A4.
  Il cannabidiolo (CBD) è converti a 7-OH-CBD, che costituisce il derivato più importante; sono poi stati identificati circa una trentina di altri derivati.

Escrezione

- **L'escrezione dei cannabinoidi avviene sia attraverso i reni (un terzo dei metaboliti) sia con le feci (2 terzi dei metaboliti)** ed è più rapida negli utilizzatori cronici di Cannabis.
- Una riduzione della funzionalità renale od epatica potrebbe comportare un aumento dei livelli plasmatici di THC e CBD o di metaboliti psicoattivi.

Legge n. 38/2010

«cure palliative»: l'insieme degli interventi terapeutici, diagnostici e assistenziali, rivolti sia alla persona malata sia al suo nucleo familiare, finalizzati alla cura attiva e totale dei pazienti la cui malattia di base, caratterizzata da un'inarrestabile evoluzione e da una prognosi infausta, *non risponde più a trattamenti specifici*



DECRETO 9 novembre 2015 . Funzioni di Organismo statale per la cannabis previsto dagli articoli 23 e 28 della convenzione unica sugli stupefacenti del 1961, come modificata

Allegato "A"

SCHEDA DI SEGNALAZIONE DI DIAGNOSI E PIANO TERAPEUTICO DI SPECIALITA' E/O PREPARATI GALENICI A BASE DI CANNABINOIDI

Nome e Cognome _____ (Iniziali ove previsto)

Numero tessera sanitaria dell'Assistito _____ Codice Fiscale _____

Data di nascita ____/____/____ Sesso M F ASL / Distretto Socio Sanitario Assistito _____

Comune di residenza dell'Assistito _____ Provincia _____ Regione _____

DIAGNOSI

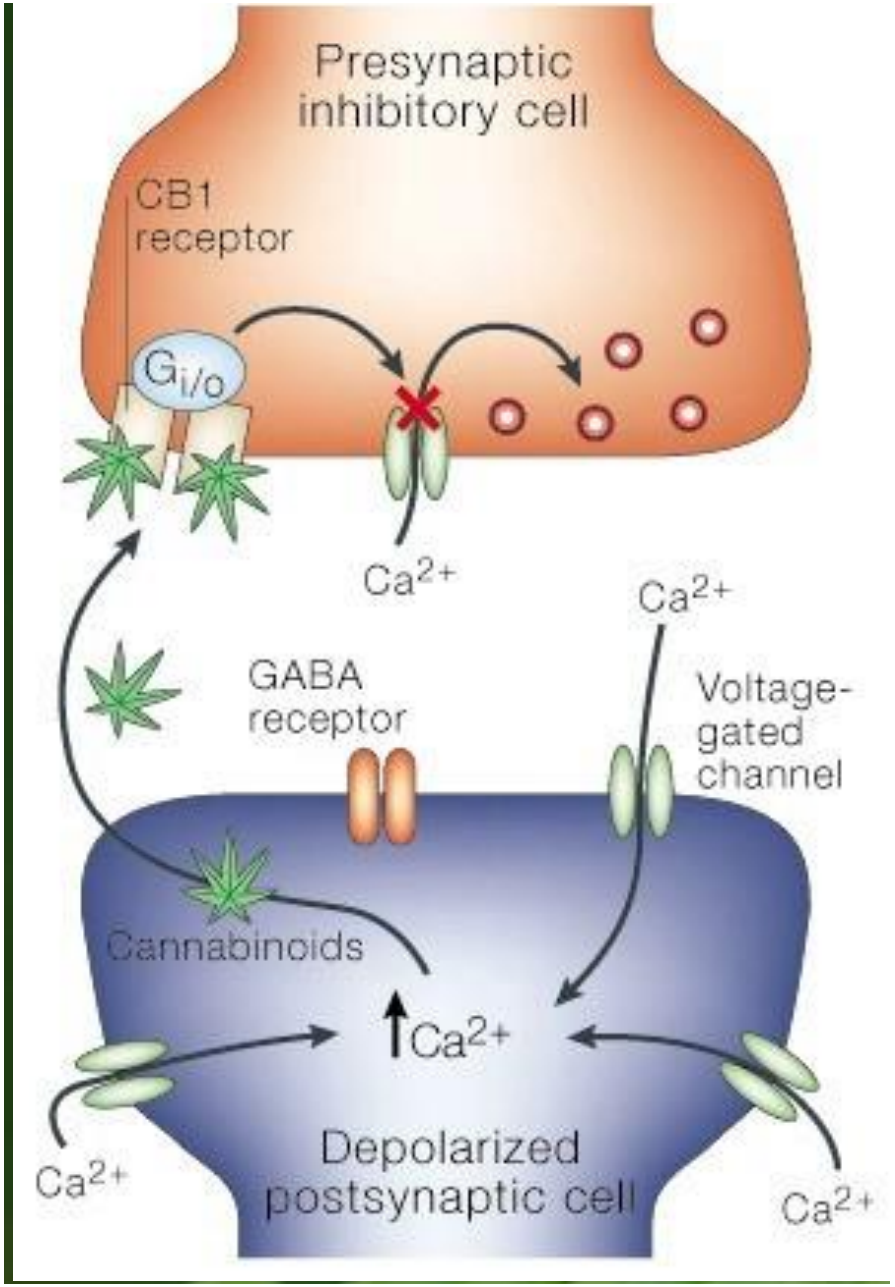
- ☐ l'analgesia in patologie che implicano spasticità associata a dolore (sclerosi multipla, lesioni del midollo spinale) resistenti alla terapia tradizionale;
- ☐ l'analgesia nel dolore cronico (con particolare riferimento al dolore neurogeno) in cui il trattamento con antiinfiammatori non steroidei o con farmaci cortisonici o oppioidi si sia rilevato inefficace;
- ☐ l'effetto anticinetosico e antiemetico nella nausea e vomito causati da chemioterapia , radioterapia, terapia per Hiv, che non può essere ottenuto con trattamenti tradizionali;
- ☐ l'effetto stimolante dell'appetito nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici, affetti da Aids, e nell'anoressia nervosa, che non può essere ottenuto con trattamenti tradizionali;
- ☐ l'effetto ipotensivo nel glaucoma resistente alle terapia convenzionali;
- ☐ la riduzione dei movimenti nella sindrome di Gilles de la Tourette;

DOLORE NEUROPATICO

- I recettori **CB1** si trovano in quantità elevate nelle zone del sistema nervoso centrale (SNC) che hanno un ruolo importante nella trasmissione e modulazione del dolore (**sostanza grigia periacqueduttale, midollo rostrale ventro-mediale e corna posteriori del midollo spinale).**

- I recettori **CB1** sono stati identificati anche a livello dei neuroni afferenti primari, sia sulle **fibre di tipo C,** che su quelle Aβ e Aδ e sui gangli della radice dorsale.
- Sulle **fibre Aδ,** coinvolte in modo importante in molti meccanismi del dolore neuropatico, *si riscontra inoltre una predominanza di recettori cannabinoidi rispetto a quelli oppioidi.*

- Durante lo sviluppo del dolore cronico neuropatico si assiste ad un aumento del numero di recettori CB2 sulla microglia, segno che le cellule stanno cercando di captare la maggior quantità possibile di cannabinoidi presenti per alleviare il dolore.
- **La stimolazione dei recettori CB2 attenua quindi l'attivazione della microglia e il rilascio di citochine.**


Presynaptic
inhibitory cell
CB1
receptor
$G_{i/o}$
Ca^{2+}
Ca^{2+}
GABA
receptor
Voltage-
gated
channel
Cannabinoids
Ca^{2+}
Ca^{2+}
Depolarized
postsynaptic cell
Ca^{2+}

DOLORE NEUROPATICO

- All'interno delle Linee Guida EFNS (European Federation of Neurological Societies) sul trattamento del dolore neuropatico (Attal et al, 2010), i cannabinoidi (THC e THC/CBD) hanno una **evidenza A per efficacia nel dolore centrale da SM**, anche se attualmente sono considerati di terza linea per i casi refrattari, considerato il limitato numero di studi a supporto (Whithing PF, 2015).

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Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain

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REVIEW

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Systematic review and meta-analysis of cannabinoids in palliative medicine

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Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD)

Phillip Good[1*], Alison Haywood[2,3], Gauri Gogna[4], Jennifer Martin[5,6], Patsy Yates[7,8], Ristan Greer[9] and Janet Hardy[10]

Abstract

Background: Despite improvements in medical care, patients with advanced cancer still experience substantial symptom distress. There is increasing interest in the use of medicinal cannabinoids, but there is little high quality evidence to guide clinicians. This study aims to define the role of cannabidiol (CBD) in the management of symptom burden in patients with advanced cancer undergoing standard palliative care.

Methods and design: This study is a multicentre, randomised, placebo controlled, two arm, parallel trial of escalating doses of oral CBD. It will compare efficacy and safety outcomes of a titrated dose of CBD (100 mg/mL formulation, dose range 50 mg to 600 mg per day) against placebo. There is a 2-week patient determined titration phase, using escalating doses of CBD or placebo to reach a dose that achieves symptom relief with tolerable side effects. This is then followed by a further 2-week assessment period on the stable dose determined in collaboration with clinicians.

Discussion: A major strength of this study is that it will target symptom burden as a whole, rather than just individual symptoms, in an attempt to describe the general improvement in wellbeing previously reported by some patients in open label, non controlled trials of medicinal cannabis. Randomisation with placebo is essential because of the well-documented over reporting of benefit in uncontrolled trials and high placebo response rates in cancer pain trials. This will be the first placebo controlled clinical trial to evaluate rigorously the efficacy, safety and acceptability of CBD for symptom relief in advanced cancer patients. This study will provide the medical community with evidence to present to patients wishing to access medicinal cannabis for their cancer related symptoms.

Research

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

JAMA 2015; 313(24):2456-73

Considerati 28 studi su efficacia dei cannabinoidi su NAUSEA e VOMITO da CHEMIOTERAPIA

Esiste evidenza che i cannabinoidi sono utili nel trattamento di Nausea e Vomito associati a Chemioterapia

Table 1. Cannabis for cancer- and cancer treatment-related toxicities: a summary.

Symptom	Conclusion
Nausea and vomiting	There is evidence that cannabis or cannabis-derived products can alleviate chemotherapy-induced nausea and/or vomiting, and an inhalable form could be better for patients unable to retain oral medications. However, most data are from the 1980s, and cannabis has not been compared with modern anti-emetic regimens.
Anorexia and loss of appetite	Medical cannabis and THC specifically, have led to increased appetite in humans and laboratory animals, mostly in noncancer contexts thus far.
Pain	Research is promising for relieving pain acutely from various sources including cancer, perhaps even to reduce the dose of opiates. However, pain surfaces *via* many different mechanisms and it is not yet clear what contexts in which cannabis could have an analgesic effect.
Chemotherapy-induced peripheral neuropathy	Evidence is promising from studies in people with HIV, trauma/surgery, and diabetes as well as cancer-related animal models, but there is not yet evidence in humans with cancer.
Gastrointestinal distress	There are promising data from research in patients with inflammatory bowel disease, but none yet in patients with cancer. Diarrhea can also be a side effect of cannabis use.
Cognitive impairment	There have not been studies with cannabis for cancer-related cognitive problems. Recreational users and patients report acute complaints in memory, attention, and executive function, though long-term effects are unclear. Some studies suggest potential benefits, especially from cannabidiol.
Anxiety and depression	Most research to date is epidemiological and results are unclear.
Sleep disorders and fatigue	Very few studies have been conducted, but limited evidence suggests that cannabis is promising for alleviation of clinical sleep disorders (not yet in patients with cancer).
Cardiac, metabolic, and bone health toxicities	Too few studies have been conducted to make conclusions recommending or discouraging cannabis for these purposes.

BJCP British Journal of Clinical Pharmacology

Cannabidiol as potential anticancer drug

Paola Massi,[1] Marta Solinas,[2] Valentina Cinquina[2] & Daniela Parolaro[2]

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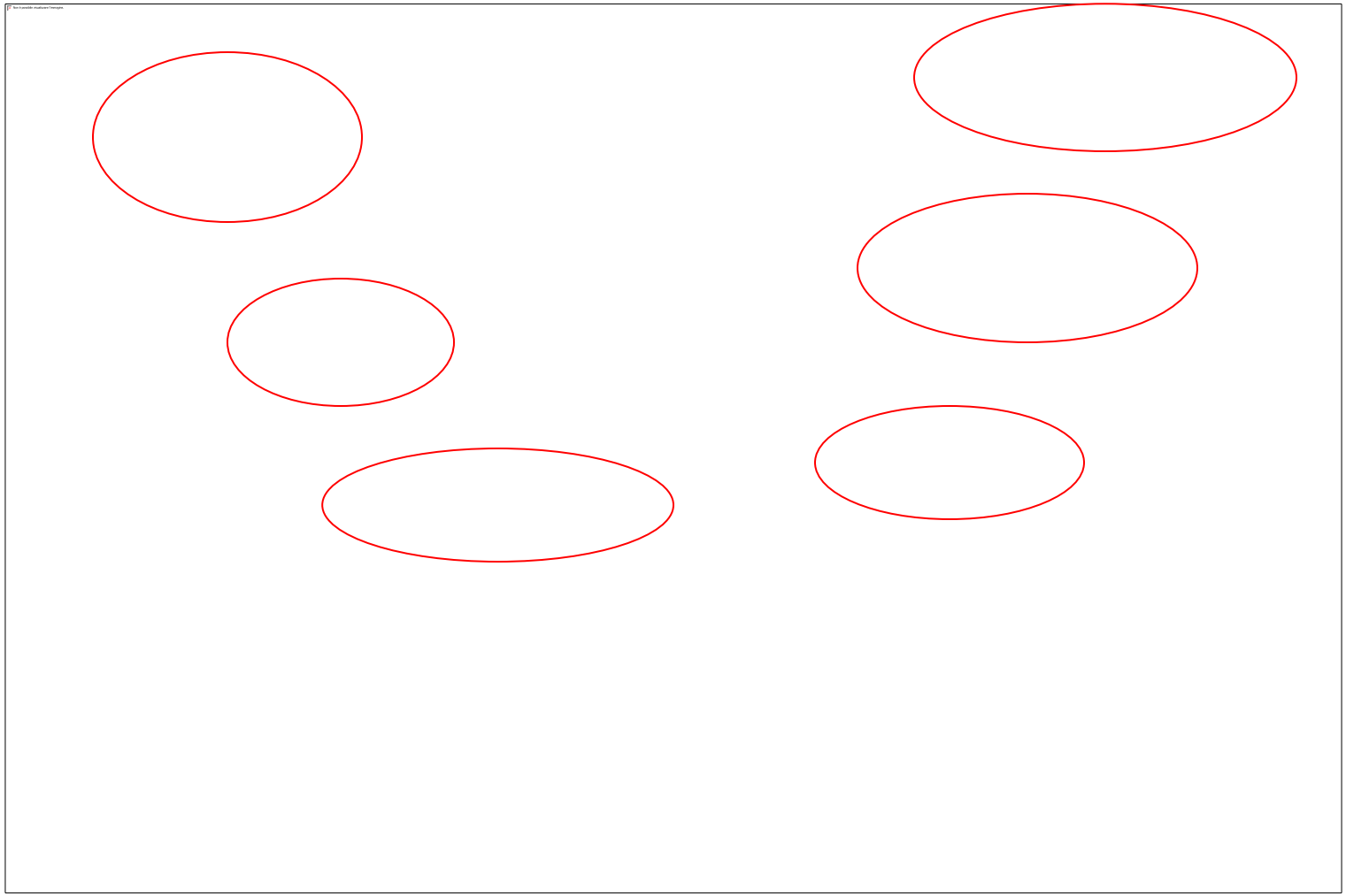

Effetti indesiderati

Non è possibile visualizzare l'immagine.

Analisi descrittiva di 25 pazienti con patologie oncologiche non più trattabili presso Ambulatorio di Terapia Antalgica (UOC Cure Palliative) PTA Bitonto ASL BA negli ultimi 3 mesi

«Se si cura una malattia, si vince o si perde; ma se si cura una persona, vi garantisco che si vince, si vince sempre, qualunque sia l'esito della terapia»