






Cannabis nell'attività terapeutica quotidiana

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CANNABIS TERAPEUTICA

LA SCINTILLA DEL CAMBIAMENTO

Responsabile Scientifico
 Professor Maurizio Cini

dal 8 SETTEMBRE al 30 DICEMBRE 2021

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LORENZO GALUS, Milano e Pisa



FABIO FIRENZUOLI, Firenze



ANDREA CAMMISERI, Milano



GIORGIO GATTI, Roma



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Quando soffiano i venti del cambiamento,
 qualcuno costruisce muri altri costruiscono
 mulini a vento.

Proverbio Cinese

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REGIONE TOSCANA

Piano Sanitario Regionale 1996-98



“Le Aziende Sanitarie promuovono l'utilizzo, da parte dei medici ospedalieri e territoriali, di piante medicinali e loro derivati, sotto forma anche di preparazioni galeniche, ai fini terapeutici”.

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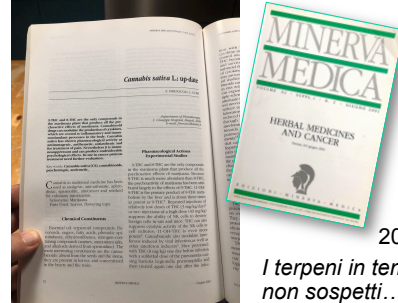


Ringrazio i miei più stretti collaboratori



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E poi ancora... Luigi Gori



2001
*I terpeni in tempi
non sospetti...*

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E poi ancora...

- * Francesco Epifani
- * Idalba Loiacono
- * Gioacchino Calapai
- * Irene Ruffino
- * Matteo Floridia
- * Mario Izzo
- * Alfredo Vannacci
- * Niccolò Lombardi
- * Giada Crescioli
- * Nadia Gulluni
- * Duccio Mediatì



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Ns ricerche

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Ricerche cliniche in corso

■ Osservazionale
Casistica AOU Careggi

■ RCT vs placebo DB
TosCannabis

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Cannabis a contenuto >>THC /CBD

Fenotipi di Cannabis terapeutica disponibili in Italia

Nome commerciale	Azienda produttrice	Distributore autorizzato/i	Varietà	THC	CBD	Terpeni
	Bedrocan BV	Acel/Comifar/Galeno/Farmalabor	Sativa	22%	<1%	ignoto
	Bedrocan BV	Acel/Comifar/Galeno/Farmalabor	Sativa	13,5%	<1%	ignoto
	Bedrocan BV	Acel/Comifar/Galeno/Farmalabor	Sativa	6,3%	8%	ignoto
	Bedrocan BV	Acel/Comifar/Galeno/Farmalabor	Sativa	<1%	9%	ignoto
	Bedrocan BV	Acel/Comifar/Galeno/Farmalabor	Indica	14%	<1%	ignoto
Pi	/1	Aurora SCFM	Sativa	17-26%	<1%	ignoto
P	/8	Aurora SCFM	Ibrida	<1%	8%	ignoto
		SCFM SCFM	Sativa	5-8%	7-12%	ignoto
		SCFM SCFM	Sativa	13-20%	<1%	ignoto

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Cannabis a contenuto >> CBD/THC

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		SCFM SCFM	Sativa	13-20%	<1%	ignoto

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Cannabis a contenuto THC = CBD

Fenotipi di Cannabis terapeutica disponibili in Italia

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Altri fattori importanti

- * Tecniche estrattive
- * Tecnica farmaceutica
- * Variabilità genetica (chemiotipi)

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Identification of Chemotypic Markers in Three Chemotype Categories of Cannabis Using Secondary Metabolites Profiled in Inflorescences, Leaves, Stem Bark, and Roots

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¹ Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada, ² PHO BioPharma Inc., Lethbridge, AB, Canada, ³ Elyon Bioscience Ltd., West Kelowna, BC, Canada, ⁴ LightHouse Genomics Inc., Salt Spring Island, BC, Canada, ⁵ Department of Electrical and Computer Engineering, University of Alberta, Edmonton, AB, Canada

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Correlations with total CBD and total THC

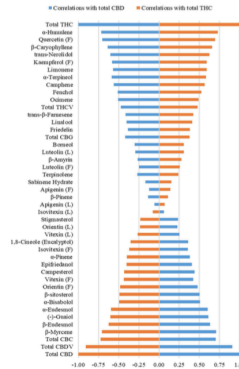


FIGURE 2 | Correlations of total THC and total CBD with cannabinoids (in inflorescences), mono- and sesquiterpenoids (in inflorescences), terpenoids (in inflorescences and leaves), terpenoids (in roots), and flavonoids (in roots) on quantitative compounds using data. Flavonoids quantified in inflorescences are labeled (F), and terpenoids in leaf are labeled (L).

Patologie neuro-degenerative

Alzheimer

Nella terapia dell'Alzheimer il **dronabinol** è risultato migliore del placebo nell'endpoint dell'aumento di peso secondo uno studio (n = 15).

Non è stato possibile trovare una differenza tra cannabis a base di erbe e cannabinoidi sintetici, analizzati da uno studio (n = 62).

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2 studi su Alzheimer



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- Uno studio incrociato con 15 partecipanti ha esaminato l'influenza del dronabinol sugli endpoint dell'effetto (**cambiamento di peso, apporto calorico e disturbi dell'umore**), tollerabilità e sicurezza.
- L'effetto del dronabinol sull'aumento di peso è stato migliore nei pazienti che hanno ricevuto prima il dronabinol e poi il placebo (p = 0,017). In entrambi i gruppi, il peso corporeo medio è aumentato durante la fase di studio. Nel gruppo placebo dronabinol di 3,95 kg, nel gruppo placebo dronabinol di 3,13 kg.
- L'apporto calorico non è cambiato nel corso dello studio. Gli affetti negativi (**rabbia, paura e tristezza**) sono diminuiti durante la terapia in entrambe le fasi dello studio (p = 0,045). Questa diminuzione è stata maggiore con la terapia con dronabinol (p = 0,004).
- Tre pazienti hanno abbandonato lo studio. Uno a causa di ADR e altri due a causa di infezioni gravi. Un paziente è morto per un attacco di cuore durante la fase placebo.

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Parkinson



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- Metodi: Da un campione di 119 pazienti valutati consecutivamente in un ambulatorio specializzato in **disturbi del movimento**, abbiamo selezionato 21 pazienti con PD senza demenza o condizioni psichiatriche comorbidie. I partecipanti sono stati assegnati a tre gruppi di sette soggetti ciascuno che sono stati trattati con **placebo, cannabidiolo (CBD) 75 mg/giorno o CBD 300 mg/giorno**. Una settimana prima dello studio e nell'ultima settimana di trattamento i partecipanti sono stati valutati rispetto a (i) punteggio motorio e generale dei sintomi (UPDRS); (ii) benessere e qualità della vita (PDQ-39); e (iii) possibili effetti neuroprotettivi (BDNF e H1-MRS).
- Risultati: non abbiamo trovato differenze statisticamente significative nei punteggi UPDRS, nei livelli plasmatici di BDNF o nelle misure H1-MRS. Tuttavia, i gruppi trattati con placebo e **CBD 300 mg/die avevano punteggi totali medi significativamente diversi nel PDQ-39** (p = 0,05).
- Conclusioni: i nostri risultati indicano un possibile effetto del CBD nel migliorare le misure di **qualità della vita** nei pazienti con PD senza comorbidità psichiatriche; tuttavia, sono necessari studi con campioni più ampi e obiettivi specifici prima di poter trarre conclusioni definitive.

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Table 2. Variations in the scores of UPDRS, PDQ-39, BDNF levels and NAA/Cr between baseline and final assessment.

	Placebo	CBD 75 mg/day	CBD 300 mg/day	ANOVA (F; p) or Kruskal-Wallis test (p)
	Variation/Baseline-Final (DP)	Variation/Baseline-Final (DP)	Variation/Baseline-Final (DP)	
UPDRS total on	3.83 (s.d.85)	3.00 (s.d.97)	6.57 (s.d.83)	F=0.633; p=0.544
UPDRS part I	0.17 (s.d.75)	0.86 (s.d.97)	0.29 (s.d.84)	F=0.733; p=0.493
UPDRS part II*	2.50 (s.d.18)	-1.29 (s.d.45)	2.85 (s.d.14)	p=0.146
UPDRS part III*	2.17 (s.d.23)	3.85 (s.d.37)	3.00 (s.d.16)	p=0.675
UPDRS part IV	-1.90 (s.d.19)	-0.43 (s.d.89)	0.43 (s.d.64)	F=0.666; p=0.538
PDQ-39 total	6.50 (s.d.48)*	10.00 (s.d.15)	25.57 (s.d.30)*	F=4.142; p=0.034
Mobility	4.17 (s.d.70)	5.71 (s.d.89)	19.64 (s.d.22)	F=2.574; p=0.108
ADL	-0.89 (s.d.48)*	16.07 (s.d.21)	21.43 (s.d.91)*	F=4.847; p=0.032
Emotional well-being	2.78 (s.d.10.08)	5.36 (s.d.10.12)	17.85 (s.d.21)	F=3.339; p=0.060
Stigma*	3.13 (s.d.23)	-4.44 (s.d.42)*	15.18 (s.d.37)*	p=0.038
Social support*	0.00 (s.d.15.64)	2.38 (s.d.12.47)	5.95 (s.d.12.47)	p=0.694
Cognition*	13.57 (s.d.72)	14.29 (s.d.56)	7.14 (s.d.31)	p=0.332
Communication	0.00 (s.d.11.79)	0.00 (s.d.5.57)	9.52 (s.d.77)	F=0.657; p=0.531
Physical discomfort	13.89 (s.d.15.52)	5.95 (s.d.19.38)	23.81 (s.d.28)	F=1.325; p=0.292
BDNF levels	-1.98E-01 (s.d.1E+05)	822.07 (s.d.86E+09)	-5.50E-01 (s.d.99E+18)	F=2.195; p=0.495
H1-MRS				
NAA/Cr right*	0.11 (0.18)	0.11 (0.18)		p=0.875
NAA/Cr left	0.19 (0.18)	-0.01 (0.07)	0.07 (0.22)	F=1.895; p=0.183

*Nonparametric distribution; *p<0.05; Bonferroni's post hoc test.

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Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease

Stephanie Martins de Faria¹, Daiane de Moraes Fabricio², Vitor Tumas³, Paula Costa Castro³, Moacir Antonelli Pontti⁴, Jaime EC Hallak⁵, Antonio W Zuardi⁶, José Alexandre S Crippa³ and Marcos Hortes Nishara Chagas¹



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- Il cannabidiolo (CBD) è uno dei componenti principali della Cannabis sativa e ha proprietà ansiolitiche, ma non è stato condotto alcuno studio per valutare gli effetti del CBD sui segni e sintomi di ansia nei pazienti con malattia di Parkinson (MdP). Questo studio mirava a valutare gli impatti della **somministrazione acuta** di CBD a una dose di **300 mg** su misure di **ansia** e **tremori** indotti da un test simulato di parlare in pubblico (SPST) in individui con PD.
- Metodi: è stato condotto uno studio clinico crossover randomizzato, in **doppio cieco**, **controllato con placebo**. Sono stati inclusi un totale di 24 individui con PD e sono stati sottoposti a due sessioni sperimentali entro un intervallo di 15 giorni. Dopo aver assunto CBD o un placebo, i partecipanti sono stati sottoposti a SPST. Durante il test sono stati raccolti i seguenti dati: frequenza cardiaca, pressione sanguigna sistemica e frequenza e ampiezza del tremore. Inoltre, sono state applicate le Visual Analog Mood Scales (VAMS) e le Self-Dichiarazioni durante il Public Speaking Scale. L'analisi statistica è stata eseguita mediante analisi della **varianza a misure ripetute (ANOVA)** considerando il farmaco, la fase SPST e le interazioni tra queste variabili.
- Risultati: c'erano differenze statisticamente significative nel fattore di ansia VAMS per il farmaco; il **CBD ha attenuato l'ansia indotta sperimentalmente** dall'SPST. **L'ANOVA a misure ripetute ha mostrato differenze significative** nel farmaco per la variabile correlata all' **ampiezza del tremore** come registrato dall'accelerometro.
- Conclusione: la somministrazione acuta di CBD alla dose di 300 mg ha ridotto l'ansia nei pazienti con PD e si è verificata anche una **diminuzione dell'ampiezza del tremore in una situazione ansigena**.

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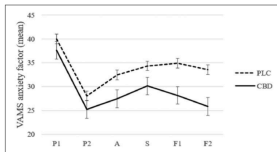


Figure 1. Comparison of CBD versus PLC administration for VAMS anxiety factor. Points in the curves indicate the positive and negative measures of the standard error. There was a significant difference between drug treatments ($n=23$). A: anticipatory; B: baseline; CBD: cannabidiol; F1: post-stress 1; F2: post-stress 2; P: pre-stress; PLC: placebo; S: performance.

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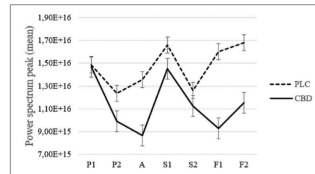


Figure 2. Comparison of the CBD versus PLC administration for the PSP characteristic measured by the accelerometer. Points in the curves indicate the positive and negative measures of the standard error. There was a significant difference between drug treatments ($n=23$). S1: start of the speech; S2: continuation of the speech.

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Syst rev

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SYSTEMATIC REVIEW

Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome

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- Cinquecentosettanta record sono stati identificati dalla ricerca nel database e nel registro di prova. **57 studi** sono stati recuperati per una valutazione dettagliata, di cui **42** sono stati infine inclusi per la revisione. Pazienti di età sia pediatrica che adulta.
- CBD puro** è stato somministrato a dosaggi fino a **50 mg/kg/giorno**. In uno studio controllato randomizzato in doppio cieco in pazienti con sclerosi tuberosa complessa, il CBD è stato associato a una riduzione percentuale significativamente maggiore della frequenza delle crisi rispetto al placebo durante il periodo di trattamento. Studi in aperto hanno suggerito l'efficacia del CBD nel trattamento di bambini e adulti che si presentano con altre sindromi epilettiche rispetto a quelle affrontate da studi normativi, tra cui il disturbo da deficienza CDKL5 e le sindromi di Aicardi, Dup15q e Doose, l'encefalopatia SYNGAP1 e l'epilessia con mioclonia assenze.
- Eventi avversi durante il trattamento: sonnolenza, diminuzione dell'appetito, diarrea e aumento delle aminotransferasi sieriche.
- La risposta al trattamento con una soluzione a base di olio di CBD di origine vegetale altamente purificata può essere osservata in pazienti con un'ampia gamma di disturbi dell'epilessia ed eziologie. Le prove esistenti possono fornire un supporto preliminare per ulteriori ricerche.

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Dolore

Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis

Herman Johal¹, Tahira Davji², Yaping Chang³, Jonathan Simone³, Christopher Vannabouathong⁴ and Mohit Bhandari⁵

¹Center for Evidence-Based Orthopaedics, Division of Orthopaedics, Department of Surgery, McMaster University, Hamilton, ON, Canada; ²OrthoEvidence Inc., Burlington, ON, Canada; ³Aphria Inc., Leamington, ON, Canada;

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SAGE

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- I dati sono stati raggruppati tramite meta-analisi con diverse durate di trattamento (2 settimane, 2 mesi, 6 mesi) e stratificati per via di somministrazione (affumicata, per mucosa orale, orale), condizioni e tipo di cannabinoidi.
- **PRINCIPALI RISULTATI E MISURE:** dolore ed eventi avversi (EA) riferiti dal paziente. Inclusi 36 lavori (4006 partecipanti), esaminando cannabis fumata (4 prove), spray di cannabis per mucosa orale (14 prove) e cannabinoidi orali (18 prove).
- Rispetto al placebo, i cannabinoidi hanno mostrato una significativa riduzione del dolore che è stata maggiore con una durata del trattamento da 2 a 8 settimane (differenza media ponderata su una scala analogica visiva del dolore 0-10 -0.68, intervallo di confidenza 95% [CI] - da 0.96 a -0.40, I² = 8%, P < 0,00001; n = 16 prove).
- I **cannabinoidi orali** hanno mostrato una riduzione del dolore maggiore rispetto al placebo rispetto alle formulazioni per mucosa orale e affumicate, ma la differenza non era significativa. Riduzione minore del dolore dovuto alla sclerosi multipla rispetto al placebo rispetto ad altri dolori neuropatici entro 2 settimane e la differenza non era significativa rispetto al dolore dovuto all'artrite reumatica. Il nablone ha avuto una maggiore riduzione del dolore rispetto al placebo rispetto ad altri tipi di cannabinoidi per più di 2 settimane di trattamento, ma la differenza non è stata significativa.
- Gli eventi avversi gravi erano rari e simili tra i gruppi cannabinoidi (74 su 2176, 3,4%) e placebo (53 su 1640, 3,2%). C'è stato un aumento del rischio di **eventi avversi non gravi** con i cannabinoidi rispetto al placebo.
- **CONCLUSIONE:** C'erano prove moderate a supporto dei cannabinoidi nel trattamento del dolore cronico non oncologico a 2 settimane. Risultati simili sono stati osservati in momenti successivi, ma la confidenza in effetti è bassa.

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Schwerpunkt

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Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis)

A systematic review of randomized controlled trials

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- La scarsa quantità e qualità dei dati disponibili sull'efficacia, la tollerabilità e la sicurezza dei cannabinoidi nel dolore cronico refrattario al trattamento convenzionale associato alle malattie reumatiche non consente alcuna raccomandazione attuale per l'uso clinico di routine. A parte una debole raccomandazione per una sperimentazione di una preparazione farmacologica di cannabinoidi in pazienti con FMS nel contesto di importanti disturbi del sonno nelle linee guida FMS canadesi, **non ci sono altre linee guida attuali** per l'uso di qualsiasi preparato cannabinoidi nella gestione del dolore cronico associato a malattie reumatiche. Questa scarsità di prove persiste nonostante l'uso millenario della cannabis in varie forme per la gestione del dolore e di altri sintomi. L'esperienza medica aneddotica e la difesa personale non possono sostituire la pratica clinica razionale basata sull'evidenza, sottolineando un appello **urgente** per **ulteriori ricerche di alta qualità**, sia a livello clinico che fisiologico.
- In ambito clinico, può essere presa in considerazione una sperimentazione a breve termine dell'uso off-label del **nablone** per quei pazienti con FMS che sono refrattari a trattamenti fisici, psicologici e farmacologici stabiliti (raccomandati dalle linee guida), all'interno di un approccio di trattamento dei componenti.
- Qualsiasi trattamento continuato con nablone deve essere guidato e bilanciato da obiettivi di trattamento predefiniti (ad es. miglioramento sostanziale del dolore e/o dei problemi del sonno e/o della disabilità) e con attenzione agli effetti collaterali emergenti. I pazienti con malattie reumatiche che richiedono un trattamento con cannabis a base di erbe dovrebbero essere informati dell'attuale assenza di prove per l'effetto e la cannabis a base di erbe dovrebbe essere riservata a quei pochi pazienti che hanno veramente esaurito le modalità basale sull'evidenza e raccomandate dalle linee guida e rimangono gravemente sintomatici e disabili.

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Table 2 Summary of efficacy in single studies

Study	Treatment	Efficacy outcomes at the end of treatment
Biale 2006	One to six activations of an oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per activation versus placebo spray	50% pain reduction: Not reported PGIC: Not assessed Pain (morning at end): THC/CBD mean 3.1 (SD NR), placebo mean 4.1 (SD NR) (p=0.02) Sleep: THC/CBD mean 3.4 (SD NR), placebo mean 4.6 (SD NR) (p=0.03) Fatigue: not assessed Depression: not assessed Anxiety: not assessed Health-related quality of life: not assessed
Prager 2006	Nablone 0.25-1 mg tid orally, flexible	DAS 28: THC/CBD mean 5.0 (SD NR), placebo mean 5.9 (SD NR) (p=0.002) 50% pain reduction: not reported PGIC: not assessed Pain reduction (current in spine): nablone median 5.9 (SD NR), placebo median 6.5 (SD NR) (p=0.20) Sleep: not assessed Fatigue: not assessed Depression: not assessed Anxiety: not assessed Health-related quality of life (Improvement): nablone median 5.0 (SD not reported), placebo median 2.0 (SD not reported) (p=0.96)
Sinabes 2008	Nablone 1 mg bid orally versus placebo Titration from 0.5 to 1 mg bid from week 1 to 4	50% pain reduction: not reported and not provided on request PGIC: not assessed Pain: nablone mean 4.8 (SD 2.2), placebo mean 5.7 (SD 1.8) (p=0.02) Sleep: not assessed Fatigue: no significant difference ^a Depression: no significant difference ^a Anxiety: nablone mean 4.3 (SD 1.8), placebo mean 4.9 (SD 2.2) (p=0.01) Health-related quality of life: mean 54 (SD 12), placebo mean 54 (SD 13) (p=0.07)
Ware 2010	Nablone 0.5 or 1 mg versus amitriptyline 10 or 20 mg at bedtime each Titration in each of 2 periods of 2 weeks, with 2 weeks washout	50% pain reduction: not reported and not provided on request PGIC: not assessed Average pain intensity: no significant difference ^a Sleep: nablone mean 9 (SD 10.8), amitriptyline mean 13 (SD 8) ^a Fatigue: not reported Depression: not reported Anxiety: not reported Health-related quality of life: no significant difference ^a



Cochrane Institute of Systematic Reviews

Neuromodulators for pain management in rheumatoid arthritis (Review)

Richard BL, White SL, Buchbinder R

Richard BL, White SL, Buchbinder R
Neuromodulators for pain management in rheumatoid arthritis
Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No. CD009705.
DOI: 10.1002/14651406.CD009705

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2012

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20 % Consumatori

RHEUMATOLOGY

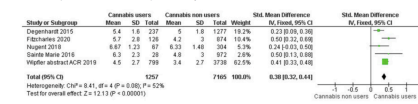
Systematic review and meta-analysis

Cannabis use assessment and its impact on pain in rheumatologic diseases: a systematic review and meta-analysis

M. Guillouard¹, N. Authier^{2,3,4}, B. Pereira⁵, M. Soubrier¹ and S. Mathieu¹

Rheumatology 2021;90:549–558
doi:10.1093/rheumatology/keaa534
Advance Access publication 7 November 2020

FIG. 3 Forest plot for the difference in pain intensity between cannabis users and non-users



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JAMA
2015

Original Investigation
Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD, Robert F. Wolf, MD, Sohan Deshpande, MSc, Marcello Di Nijs, PhD, Steven Duffy, PGD, Adrian V. Hernandez, MD, PhD, J. Christiaan Keurentjes, MD, PhD, Sheng-Lang, PhD, Kine Miso, MSc

- 

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DOI: 10.1089/jam.2010.0331

JACM

Safety and Efficacy of Medicinal Cannabis in the Treatment of Fibromyalgia: A Systematic Review

Irma Kurliyandchik, BHS,¹ Evelin Tralongo, PhD,² and Janet Schloss, PhD^{1,3,4}

Abstract

Background: Fibromyalgia (FMS) is a complex condition that is characterized by various pain syndromes and fatigue, among other symptoms experienced. Current medical treatment of FMS involves both pharmacological and nonpharmacological approaches, but often with ineffective outcomes. Medicinal cannabis has the potential to be a therapeutic option for patients with FMS due to the positive research in chronic pain management. In addition, it has been found to have fewer adverse effects compared with currently available pain medications. This literature review aims at answering whether medicinal cannabis is reported to be safe and effective for the treatment of pain and symptomatology experienced by people with FMS.

Methods: A systematic review was conducted on human trials utilizing cannabis in FMS. MEDLINE, Embase, CINAHL, AMED, Scopus, and Cochrane CENTRAL were used for databases search, and mesh terms were used for cannabis and FMS. The search was limited to studies conducted from 2000 to 2020.

Results: From the 181 citations identified, 10 studies were included after title, abstract, and full-text screening occurred. A total of 136 of patients (intervention n = 75, control n = 108, crossover n = 53) participated in the 10 studies ranging from 5 to 383 patients (mean = 114, median = 36). Of these studies, there were three randomized controlled trials, six observational studies, and one study that compared the management of chronic pain patients with FMS patients. Cannabis was found to be safe and well-tolerated in FMS. The main adverse events identified included feeling "high," dizziness/vertigo, dry mouth, cough, red eyes, and drowsiness with no serious adverse events reported.

Conclusion: This literature review identified that medicinal cannabis may be beneficial for some people with FMS. Further studies are required to confirm its efficacy, what type of cannabis is the most effective form to use, and what assessment tools need to be utilized to understand how to quantify clinical outcomes.

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Dolore

BMJ, 3 sett 2021

PRACTICE

Check for updates

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Additional material is published online only. To view please visit the journal online.
Cite this as: BMJ 2021;374:n2040
https://doi.org/10.1136/bmj.n2040

RAPID RECOMMENDATIONS

Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline

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Table 2 | Characteristics of 32 eligible randomised clinical trials included in systematic review of medical cannabis for chronic pain

Patient characteristics	Values
No. of patients enrolled*	71 (20–457)
Length of follow-up (days and months)	50 days (28–154), <2 months (0–53)
Mean age (years)†	53 (33–83)
Gender (% women)†	60 (0–100)
Trial characteristics	No. of trials; No. of patients
Types of chronic pain represented	Chronic non-cancer pain (28 trials; 3812 patients); Neuropathic (11 trials; 1665 patients); Nociceptive (2 trials; 378 patients); Nociceptive (5 trials; 230 patients); Medication overuse headache (1 trial; 60 patients); Spasticity-related (7 trials; 1999 patients); Mixed types (2 trials; 80 patients); Chronic cancer pain, non-palliative (4 trials; 1362 patients)
Type of cannabis	Phytocannabinoids (7 trials) ^{37,52} Synthetic (10 trials) ^{37,52} Endocannabinoids (5 trials) ^{62,66}
Type of cannabinoid(s) administered	THC and CBD (12 trials) ^{37,52,53,54,67} THC (10 trials) ^{37,53,54,67} CBD/CBDV (5 trials) ^{50,54,67} PEA (5 trials) ^{62,66}
Mode of administration	Oral capsule (16 trials) ^{37,53,54,61,62,67} Oral spray (3 trials) ^{37,54,67} Sublingual drops (1 trial) ⁶² Transdermal cream (2 trials) ^{50,54}
Funding source	Industry funded (21 trials) No industry funding (6 trials) Not reported (5 trials)

Population

These recommendations apply only to people with these characteristics:

All patients living with moderate to severe chronic pain

Applies to people with:

- ✓ Cancer and non-cancer pain
- ✓ Neuropathic pain, nociceptive pain, and nociceptive pain

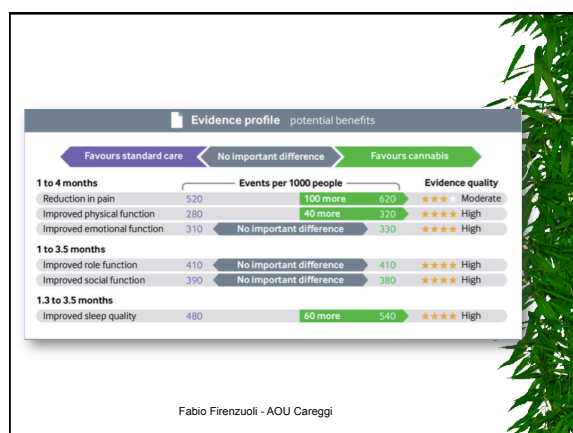
May or may not apply to:

- ? Paediatric populations
- ? Veterans
- ? Patients with concurrent mental illness
- ? Patients receiving disability benefits or involved in litigation

Does not apply to:

- ✗ Inhaled medical cannabis
- ✗ Recreational cannabis
- ✗ Patients receiving end of life care

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Box 3: Key practical issues

Medication routine

- Therapeutic trials should start with low dose, non-inhaled cannabidiol (CBD) products, gradually increasing the dose and THC level depending on clinical response and tolerability (such as starting at a dose of 5 mg CBD twice daily and increasing by 10 mg every 3–5 days to a maximum daily dose of 40 mg). If response is unsatisfactory, clinicians may consider adding 1–2.5 mg THC per day and titrating to 2.5 mg every 2–7 days to a maximum of 40 mg/day.
- Prior cannabis experience should be considered, and adverse event monitoring should be carefully conducted.
- For younger or adolescent patients, CBD-predominant preparations should be preferred because of uncertain effects of THC on neurocognitive development.

Administration

- Our evidence synthesis was largely informed by oral preparations of medical cannabis or cannabinoids, including sprays, tablets, and oil drops administered sublingually. Our recommendation does not apply to inhaled forms of cannabis, which entails pulmonary exposure to particulate matter and toxins.

Adverse effects

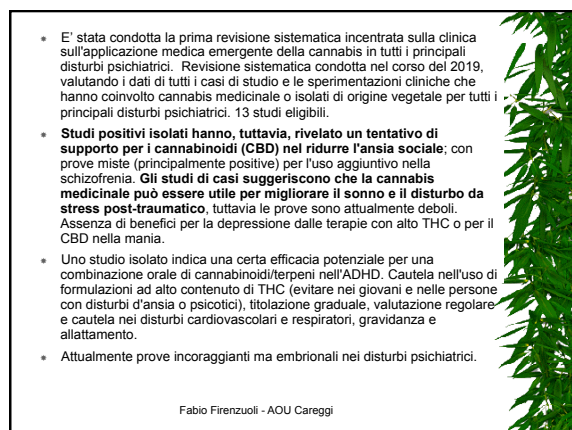
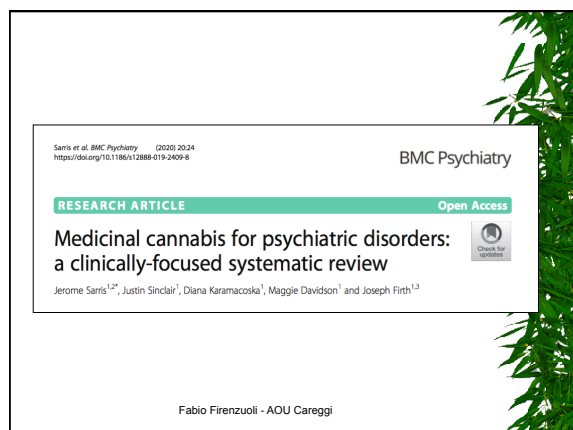
- Serious adverse events are unlikely with medical cannabis or cannabinoids, and patients cannot fatally overdose. Dizziness is the most common non-serious adverse event with medical cannabis treatment.

Pregnancy and nursing

- Evidence regarding adverse effects of medical cannabis or cannabinoids use during pregnancy or breastfeeding is inconclusive: pregnant women or women contemplating pregnancy should be encouraged to discontinue use of medical cannabis in favour of alternative therapy. Cannabis use during breastfeeding should be discouraged.

Travel and driving

- Avoid driving or operating machinery while starting or changing doses of medical cannabis or cannabinoids.



Mental Disorder	Cannabinoids Studied	Methodology	Results	Clinical Comment
Social Anxiety	Bergmachi [38] CBD 800 mg	24 treatment-naïve patients with Social Anxiety were blindly allocated to receive CBD or placebo 1 h before a simulated public speaking test. 12 unmedicated healthy controls also completed the test. Self-reports on the Visual Analogue Mood Scale and Negative Self-Statement scale, and physiological measures were taken at six time points during the test.	Pre-test CBD administration in Social Anxiety patients versus placebo, resulted in significantly reduced anxiety, cognitive impairment and discomfort in speech performance, and significantly decreased hyper-alertness in anticipatory speech. CBD and control groups however did not differ reflecting similar response profiles during the public speaking test.	The initial positive studies suggest that CBD may be a beneficial safe option in larger confirmatory study needed.
Crippa [39] CBD 400 mg		Compared regional cerebral blood flow activity in 10 treatment-naïve patients with SAD who were given CBD or placebo, in a double-blind crossover manner.	CBD compared to placebo, resulted in significantly lower subjective anxiety, and modulated blood flow in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and right posterior cingulate gyrus.	
PTSD	Greer [40] Cannabis (not defined)	Analyzed retrospectively collected CAPS data from 60 patients with PTSD.	Patients reported >75% decrease in CAPS scores when they were using Cannabis compared to periods when they were not.	No firm evidence yet, however initial case analyses suggest this application may be of benefit to manage PTSD symptoms, reduce anxiety, and improve sleep.
Elms [41] CBD (capsule or spray) mean 8 (4-49 mg)		Open label retrospective case study data from 11 adult patients with PTSD, data assessed over 8 weeks.	Mean PTSD symptoms on the PCL-5 reduced by 28%. Actual statistical data analysis not conducted.	
Depression	Potency [42] Nabiximols, THC (2.1 mg) and CBD (2.5 mg)	263 patients with advanced cancer and opioid-refractory pain were randomly allocated to receive placebo or nabiximols daily at low (1-4 spray), medium (6-10 spray) or high (11-16 spray) doses, for 4 weeks. Pretest measures included average pain, worst pain, sleep duration, quality of life and mood.	Reports of pain relief were significantly greater for nabiximols than placebo overall, especially in the low and medium-dose groups. There were no other significant group differences. Adverse events were dose-related with only the high-dose group reporting a decrease in mood.	No evidence for use in depression, however higher doses of THC predominant medicines may be of lower mood.

Insomnia	Shannon [43] CBD capsules (25 mg) + liquid (5-25 mg)	Patient (10 y.o. girl with prior early childhood trauma) was prescribed fish oil (250 mg daily) + CBD or capsule daily for 5 months. CBD liquid (1.2-24 mg) was added to the regimen for 1 month and reduced to 8-12 mg p.m. when needed. Sleep assessed monthly via SOSC.	SOSC scores decreased over the 5-month period, indicating an increase in sleep quality and quantity.	Only case study and secondary outcome evidence at present. Encouraging as a potential use pending controlled studies, however test-day effects need to be assessed in terms of performance and cognitive functioning.
	Johnson [71] Nabiximols, THC (2.1 mg) and CBD (2.5 mg) OR THC only (2.1 mg)	43 patients, with advanced cancer and opioid-refractory pain, self-administered daily nabiximols or THC only sprays for 5 weeks. Safety, tolerability, pain and quality of life were assessed.	Across groups, pain decreased at every visit and showed pre-trend improvement with insomnia and fatigue.	
	Shannon [72] CBD capsules (empty 25 mg) OR CBD capsules (empty 25 mg)	A retrospective case series of 72 adults given CBD for anxiety and sleep complaints at a psychiatric clinic, as an adjunct to usual treatment. Assessed monthly over 12 weeks.	Anxiety scores on the HAMA decreased within the first month in 79% of the sample and remained decreased during the study duration. PSQ sleep score improved within the first month in 67%, but fluctuated over time. Data appeared to not be statistically significant for the	

Schizophrenia	Leewille [44] CBD 800-800 mg	42 individuals with schizophrenia were randomly assigned to receive 800 mg of CBD or placebo over 4 weeks. The PANSS and BPRS were administered every 14 days. Blood was also collected.	Both treatments were effective in reducing PANSS and BPRS scores at each time point. CBD was tolerated better, with fewer side effects reported. Aripiprazole levels were higher in the CBD group post-treatment.	Avoid any use of high THC in youth, 600 mg + 100 mg of CBD per day may be effective as an adjunct for use in vet symptoms.
	McGuire [101] CBD (1000 mg)	88 antipsychotic-treated patients with schizophrenia were randomly given placebo or CBD alongside their antipsychotic medication for 4 weeks. Pre-test measures included the PANSS, Brief Assessment of Cognition in Schizophrenia, Global Assessment of Functioning, Clinical Global Impressions of Improvement and Severity scales.	The CBD group reported lower positive symptom scores, and were more likely to be rated as improved and less severely ill than the placebo group. The CBD group also showed improvements in the cognitive domain of motor speed compared to placebo. CBD was tolerated well with similar adverse event rates reported between the groups.	
	Boggs [102] CBD (800 mg)	36 individuals with schizophrenia were randomized to receive CBD or placebo additionally to current antipsychotic medication for 4 weeks. PANSS and MCCF were assessed pre/post trial.	Both groups showed improvement on PANSS scores and only the placebo group improved on the MCCF. Small dose effects were noted between the groups, with more robust evidence in the CBD group.	
Bipolar Disorder	Zuardi [103] CBD 800-1200 mg	Two patients with bipolar I disorder were administered CBD for 30 days with 4 days of placebo pre/post trial. Patients were assessed on the YMRS and BPRS every 7 days.	One patient showed improvements in YMRS and BPRS scores while on CBD vs. placebo but no additional improvement during CBD monotherapy. The second patient had no symptom improvement with any dose of CBD. Both tolerated CBD well with no side effects reported.	Not presently recommended. CBD appears not to be effective in attenuating mania.
ADHD	Casper [104] Nabiximols, THC (2.1 mg) and CBD (2.5 mg)	30 adults with ADHD were randomly prescribed nabiximols or placebo for 4 weeks. A participant's optimal dose was decided at day 14. The QFT assessed cognitive performance and activity level (head movements). Conners Adult ADHD Rating Scale rated ADHD symptoms and self-reports to determine emotional lability.	The nabiximols group showed an improvement in QFT scores that approached significance. No significant improvements in ADHD symptoms were also found for the nabiximols group compared to placebo.	Potentially may be effective in managing some ADHD symptoms however more research is needed. Lower THC formulae alleviate concerns about cognitive impairment.



TABLE 1: Clinical studies investigating CBD effects in schizophrenic patients.

Pharmacologic therapy	Study design	Population	Treatment	Impacts on PANSS	Outcomes	Reference
Acute schizophrenia	Randomized, double-blind, multicenter, controlled clinical trial	Sample of 22 acutely hospitalized patients with first-episode schizophrenia (mean age 26 years)	CRD or placebo, starting with 100 mg daily for 200 mg per day (50 mg per day) daily (mean 400 mg per day)	ERP and PANSS were both used as outcome for the study The CRD group had a mean decrease in baseline days 14 of 1.5 on the CRD scale The PANSS group had a mean decrease in baseline days 14 of 1.5 on the PANSS scale	CRD treatment significantly improved clinical symptoms and social functioning The CRD group had a mean decrease in baseline days 14 of 1.5 on the CRD scale The PANSS group had a mean decrease in baseline days 14 of 1.5 on the PANSS scale	Casatelli, et al. (2013)
Schizophrenia or a related disorder	Meta-analysis, double-blind, placebo-controlled	Sample of 22 acutely hospitalized patients with first-episode schizophrenia (mean age 26 years)	CRD or placebo, starting with 100 mg daily for 200 mg per day (50 mg per day) daily (mean 400 mg per day)	ERP and PANSS were both used as outcome for the study The CRD group had a mean decrease in baseline days 14 of 1.5 on the CRD scale The PANSS group had a mean decrease in baseline days 14 of 1.5 on the PANSS scale	CRD treatment significantly improved clinical symptoms and social functioning The CRD group had a mean decrease in baseline days 14 of 1.5 on the CRD scale The PANSS group had a mean decrease in baseline days 14 of 1.5 on the PANSS scale	Casatelli, et al. (2013)

CRD: cannabidiol; BPRS: Brief Psychiatric Rating Scale; EPS: Extrapyramidal Symptom Scale; PANSS: Positive and Negative Syndrome Scale; PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia.

TABLE 2: Clinical studies investigating CBD effects in social anxiety disorder (SAD).

Psychiatric disorder	Study design	Population	Treatment	Endpoints	Outcome	Reference
Generalized social anxiety disorder (SAD)	Randomized, double-blind, controlled trial	Sample: a total of 140 new-treated subjects with generalized SAD and 12 healthy control subjects	SAD patients were randomly assigned to two groups with 12 subjects each to receive CBT (600 mg) or placebo 1 hour and half an hour before the test (Healthy controls: n = 12) did not receive any medication	Simulation public speaking test (SPST) Subjective ratings on VAMS and negative affect Physiological measures (heart rate, skin conductance) were measured at six different time points during the SPST	Pretreatment with CBD significantly reduced anxiety, cognitive impairment, and discomfort in public speaking performance and significantly decreased alertness in anticipatory speech	Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients [37]
Generalized social anxiety disorder (SAD)	Randomized, double-blind, placebo-controlled crossover study	Sample 10: treatment-naïve patients with SAD aged 20–35 years (mean age 24.2 years; SD 3.7)	Active oral CBD 400 mg or placebo	Brief Social reduced ICD3 (BSPS) and Phobia Inventory (PI) ratings Heart rate, blood pressure, and skin conductance were measured twice using 59 mV r-ICD3 SPST in the right posterior cingulate	Reduction anxiety is associated with SAD patients reduced ICD3 uptake in the left periaqueductal gray (PAG), hippocampus, and inferior olive (IO) of the brainstem, and increased ICD3 uptake in the right posterior cingulate	Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: preliminary results [38]

girus

TABLE 3: Clinical studies investigating on CBD anxiolytic effect in healthy subjects

[illegible]

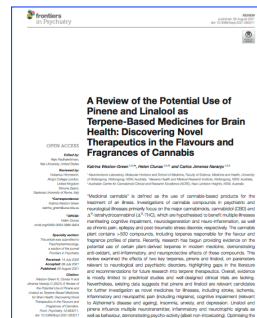
CBD = cannabidiol; delta-9-THC = delta-9-tetrahydrocannabinol



Trichomes on leaves and buds produce the cannabis plant's active compounds.

- * Mircene
- * Linanolo
- * Limonene
- * Beta cariofillene
- * ...

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Fitocomplesso

Nature 2019, S12, vol 572

- * Placebo
- * THC
- * Sativex

Johnson, J. R. et al.
J. Pain Symptom Mgmt **39**, 167–179 (2010).

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Metanalisi 2018

Epilessia

pz migliorati

- | | |
|-------------------|------|
| * CBD | 46 % |
| * CBD in Cannabis | 71 % |

Pamplona, F. A., da Silva, L. R. & Coan, A. C.
Front. Neurol. 9, 759 (2018)

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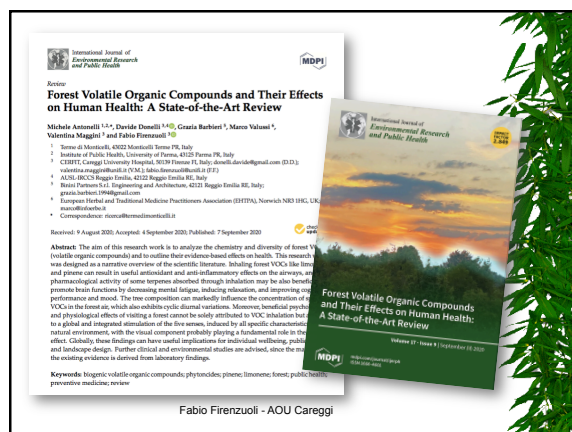
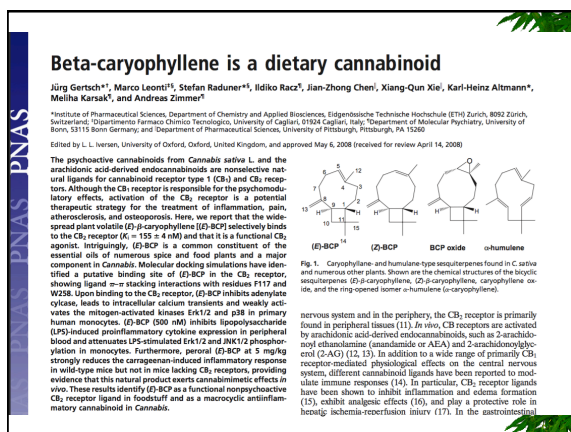
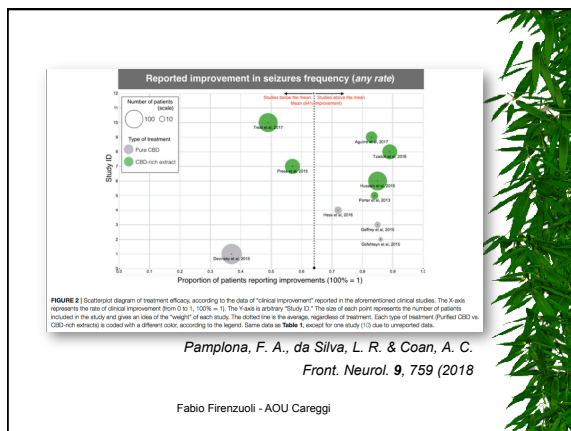


Table 9. Summary of preclinical evidence relative to biological activities of the five most common forest VOCs [3,30,34–37].

Molecule	Effects	Mechanisms	References
D-Limonene	Anti-inflammatory	It inhibits the synthesis or release of pro-inflammatory mediators (TNF-α, NO, IL-1β, IL-6, IL-8, IL-13, TGF-β) enzymes (iNOS, COX-2, iNOS), transcription factors (NF-κB), and mitogen-activated protein kinases (MAPKs) and mitogen-activated protein kinases (MAPKs) and mitogen-activated protein kinases (MAPKs).	[4,70,71,72]
	Antioxidant	It inhibits caspase-3 and increases the activities of cell antioxidant enzymes (superoxide dismutase and the Bcl-2/Bax ratio).	[4,70,72]
	Antiproliferative	It induces phase II carcinogen-metabolizing enzymes, inhibits peroxyl radical activity, increases cell autophagy (via MAP1LC8B, mitochondrial death pathway, the FEN1/Mt pathway, and caspase-3 and -9 activity) and differentiation, reduces cyclin D1 and increases TGF-β signaling, decreases tumor-induced immunosuppression, induces circulating Vascular Endothelial Growth Factor (VEGF) and blocks the receptor VEGFR-2, increases DNA damage repair and PARP cleavage. It modulates the expression of the chemokine protein MCP-1 and of the proteolytic enzymes MMP-2, MMP-9.	[4,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000]
Antinociceptive	It shows some degree of efficacy in mice and rat models.		[4,70,72,73]
	It shows some degree of efficacy in mice and rat models.		[130–134]
	It shows some degree of efficacy in mice and rat models.		[130–134]

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	Anticancer, anticancer	In several animal models, it enhances sleep by acting as a potent anxiolytic and sedative. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[10,120,220–240]
α-Pinene	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,150,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
β-Pinene	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
β-Myrcene	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
Camphor	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]
	Anticancer	It induces ROS production, causes a cell cycle arrest, and induces apoptosis, leading to cell death. It also shows anticancer activity, inhibiting cell growth and inducing apoptosis.	[140,160]

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