Cannabis, Cancer and Chronic Pain. Exploring the Connections.

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IS THERE EVIDENCE THAT CANNABIS CAN BE USED THERAPEUTICALLY FOR CANCER? CONTRAINDICATIONS?

IS CANNABIS EFFECTIVE FOR CHRONIC PAIN MANGEMENT? IS IT SAFE?

ORAL IMPLICATIONS FOR CANNABIS USAGE?

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Complex

Chemistry, Psychoactive vs Non-psychoactive, Methods of Usage, Dosing, Strains, Cultivators, Age, etc.

Conflicting

Published Data, State Laws Variations, Lack of FDA Regulation, Unmet Medical Need vs Potential Harm

Confusing

Terminology - all over the map! Vernacular in the Industry, Anecdotal data, Polarizing Topic

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Abbreviations

THC	tetrahydrocannabinol	TRP	transient receptor potential
CB	cannabinoid	MS	multiple sclerosis
THCA	tetrahydrocannabinolic acid	CINV	chemotherapy-induced nausea and vomiting
CBDA	cannabidiolic acid	BBB	blood–brain barrier
CBNA	cannabinolic acid	HER2	human epidermal growth factor receptor 2
CBGA	cannabigerolic acid	FAAH	fatty acid amide hydrolase
CBCA	cannabichromenic acid	MAGL	monoacylglycerol lipase
CBNDA	cannabinodiolic acid	VEGF	vascular endothelial growth factor
GPP	geranyl pyrophosphate	ERK	extracellular signal-regulated kinase
OLA	olivetolic acid	MAPK	p38 mitogen-activated protein kinase
GOT	geranyl-diphosphate:olivetolate geranyltransferase	Nupr1	stress-related nuclear protein 1
THCAS	tetrahydrocannabinolic acid synthase	ATF4	activating transcription factor 4
CBDAS	cannabidiolic acid synthase	CHOP	C/EBP homologous protein
CBCAS	cannabichromenic acid synthase	TRIB3	tribbles pseudokinase 3 protein
TRPV1	transient receptor potential cation channel subfamily V	mTORC1	mammalian target of rapamycin complex 1
GPR	G protein-coupled receptors	ER	endoplasmic reticulum
PPARs	peroxisome proliferator-activated receptors	TRP	transient receptor potential channel
ES	endocannabinoid system	GPR	G protein-coupled receptor
CBRs	CB receptors	AMPK	AMP-activated protein kinase
AEA	N-arachidonoylethanolamine	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2
2-AG	2-arachidonoylglycerol	CDK	cyclin-dependent kinases
SCBs	Synthetic cannabinoids	BAD	Bcl-2-associated death promoter
GPCR	G-protein coupled receptor	Bcl-2	B-cell lymphoma 2 protein
cAMP	adenosine monophosphate	ROS	reactive oxygen species
MAPK	mitogen-activated protein kinase	TRPM8	transient receptor potential cation channel subfamily M member 8
PI3K	phosphoinositide 3-kinase	CBG	cannabigerol
COX-2	cyclooxygenase-2	Id1	inhibitor of differentiation 1 protein
CNS	central nervous system	ICAM-1	intercellular adhesion molecule 1
		TIMP-1	tissue inhibitor of matrix metalloproteinases-1
		LAK	lymphokine-activated killer

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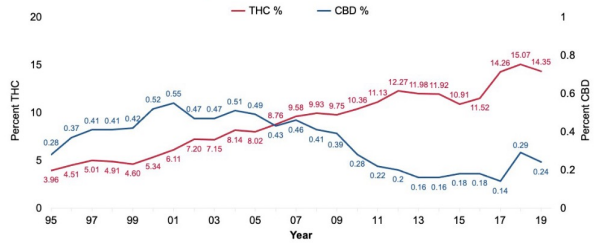
Percentage of THC and CBD in cannabis samples seized by the DEA from 1995-2019



www.drugabuse.gov

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Government of Canada / Gouvernement du Canada

Legal cannabis:

- is quality controlled and tested for harmful levels of contaminants
- is tested for accuracy of THC and CBD levels, so you know exactly what you're buying
- can be recalled by manufacturers, licence holders or Health Canada if there's a potential safety or quality issue

Illegal cannabis:

- is **not** tested or quality controlled and may contain harmful levels of contaminants, including:
  - heavy metals
  - pesticides
  - mould
  - cutting agents
  - bacteria

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/personal-use/reduce-risk-choose-legal.html

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1. Standardized cannabis symbol (>10 micrograms)
2. Product brand name
3. Excise stamp (low THC and Rx cannabis not required)
4. THC & CBD amount (By weight, by units/servings by activation)
5. Health warning message (effects can be long-lasting: 6-12 hours)
6. Other required information (Equivalent of number of g of dried cannabis)

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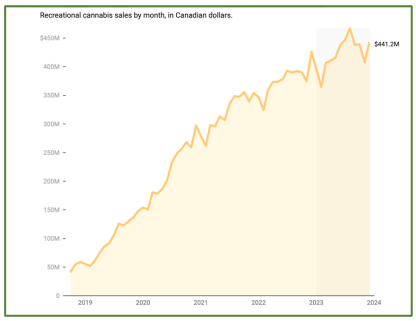
2023 Cannabis recreational sales worth: $5.07 Billion (Canadian)

12.2% increase from 2022

~40% of cannabis market sales still illicit market

Edibles limit 10g THC per pkg



www.mjbizdaily.com

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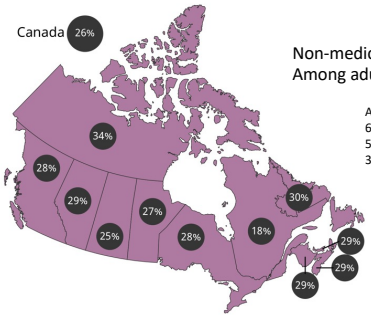

Non-medical use of cannabis in 2024
Among adults 16+

Among those using in past 12 months:
69% reported Smoking
57% reported Eating/Drinking
37% reported Vaping

Source: Canadian Cannabis Survey.
health.infobase-Canada.ca

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Why do you think cannabis sales dropped in 2024 in Canada?

Edibles down 12.4%
Flowers down 9.3%
Total cannabis revenue down 3.27%

www.mjbizdaily.com

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CANNABIS 101 – it's a plant

"Hemp" < 0.3% THC

"Marijuana"/"Cannabis" > 0.3% THC

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"Godfather of Cannabis Research"

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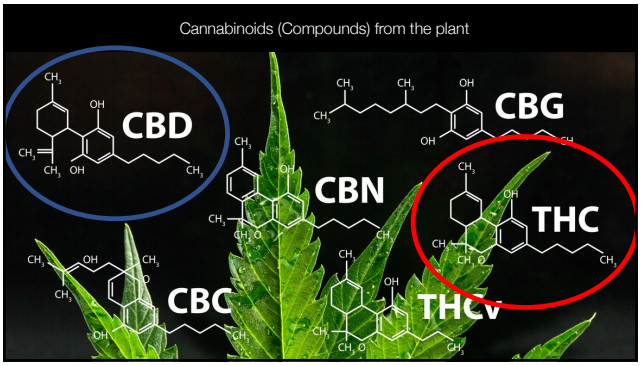

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Cannabaceae

Cannabaceae comprises the following genera:

- Aphananthe Planch. (5 spp.)
- Cannabis —Hemp (3 spp.)
- Celtis L. (73–109 spp.) Ornamental trees
- Chaetachme Planch. (1 sp.)
- Gironniera Gaudich. (6 spp.)
- Humulus L. —Hop (3 spp.) Beer
- Lozanella Greenm. (2 spp.)
- Parasponia Miq. (5–10 spp.)
- Pteroceltis Maxim. (1 sp.) Rice paper
- Trema Lour. (12–42 spp.)

~170 Species

Medicinal use: China 494 B.C.

Jiang, Hong-En; Li, Xiao; Zhao, You-Xing; Ferguson, David K.; Hueber, Francis; Bera, Subir; Wang, Yu-Fei; Zhao, Liang-Cheng; Liu, Chang-Jiang & Li, Cheng-Sin (December 2006). "A new insight into Cannabis sativa (Cannabaceae) utilization from 2500-year-old Yanghai Tombs, Xinjiang, China". Journal of Ethnopharmacology. 108 (3): 414–422. doi:10.1016/j.jep.2006.05.034. PMID 16920297.

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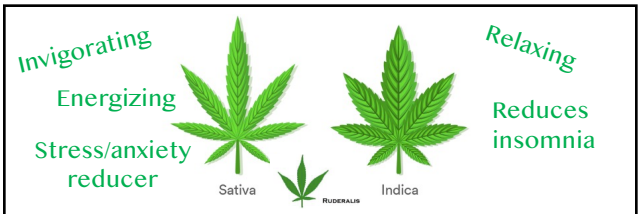

"Strains" Referred to as "CHEMOVARS"

TYPE I: High THC

TYPE II: THC/CBD combined

TYPE III: High CBD

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healthline

Strains to consider for certain conditions

Strain	Category	CBD	THC	Conditions
Acapulco Gold	sativa	0.1%	15–23%	• fatigue • stress • nausea • pain
Blue Dream	hybrid	less than 1%	30%	• pain • cramps • inflammation • insomnia • mental fog • PTSD
Purple Kush	indica	less than 1%	17–22%	• chronic pain • muscle spasms • insomnia
Sour Diesel	sativa	less than 1%	20–22%	• fatigue • stress • acute pain • mental fog • anxiety • PTSD
Bubba Kush	indica	less than 1%	14–25%	• insomnia • acute pain • nausea • low appetite • PTSD

https://www.healthline.com/health/sativa-vs-indica#cannabis-strain-chart

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CONCENTRATES

MOST FLOWERS 15-25% THC

THC CONCENTRATES 80-90%

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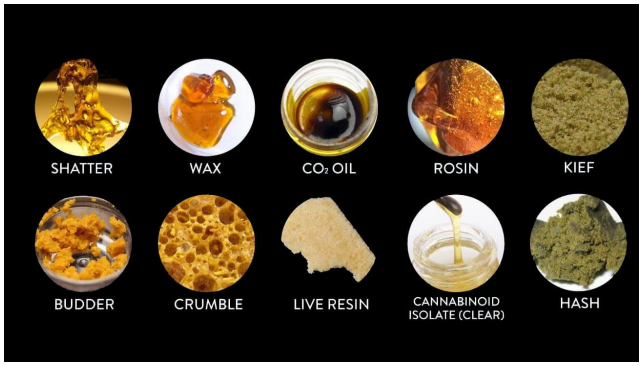

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Oral Cannabis can have long duration (up to 8 hours), onset can be erratic depending upon absorption & foods

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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Smoking most common use with rapid onset (10 minutes) and duration 2-4 hours

Combustion at extremely high temperatures produces toxic byproducts, and chronic use is associated with respiratory symptoms

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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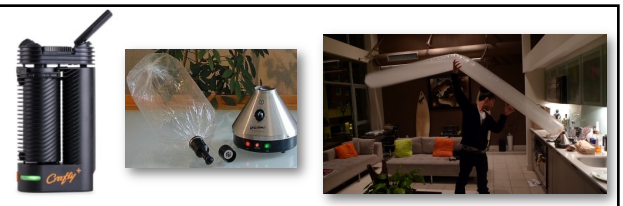

"Vaporizers are safe and efficient devices that are temperature controlled to decarboxylate inactive cannabinoids and release active, potent cannabinoid compounds"

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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Selective Breeding = THC Variations

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Terpenes – Aromas, Smell, Color, Taste

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Medicinal Properties of terpenes from different sources

Terpene	Medicinal properties	References
Tea tree	Contains the active ingredient to treat cutaneous infections	Carson et al. (2006)
Thyme	Possesses powerful antibacterial and antifungal properties	Bound et al. (2015)
Cannabis	Possesses psychoactive properties and used against many infectious diseases	Friedman et al. (2006)
Spanish sage	Enhances memory and is used in anti-dementia drugs	Lopresti (2016)
Citrus fruits	Drugs against pediculosis	Mehlhorn et al. (2011)
Citral	Antibacterial and antifungal effects	Silva et al. (2008)
Lemongrass	Insect repellent	Silva et al. (2008)

Cox-Georgian D, Ramadoss N, Dona C, Basu C. Therapeutic and Medicinal Uses of Terpenes. *Medicinal Plants*. 2019;333-359. Published 2019 Nov 12. doi:10.1007/978-3-030-31269-5_15

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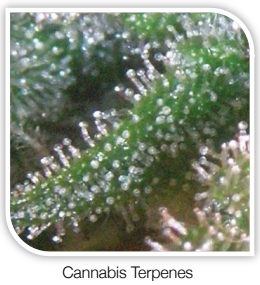
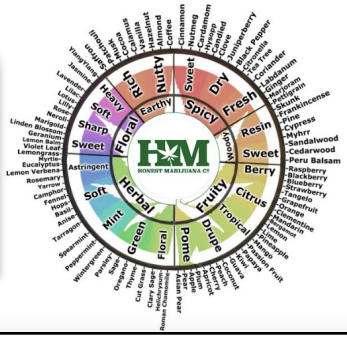


Cannabis Terpenes



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"Entourage Effect"

THCA,
CBD, CBDA,
CBN, CBC, CBG

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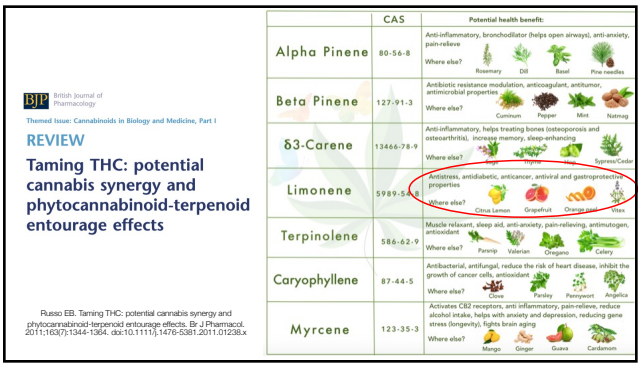

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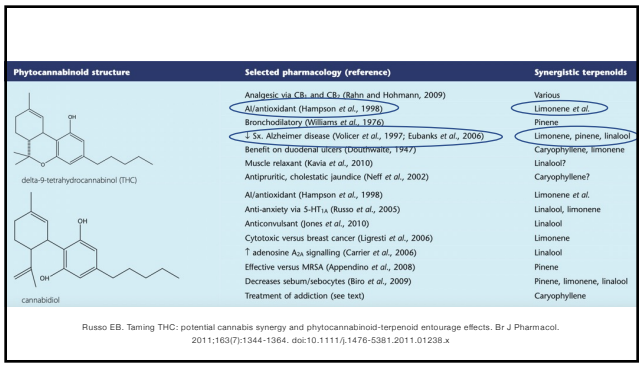

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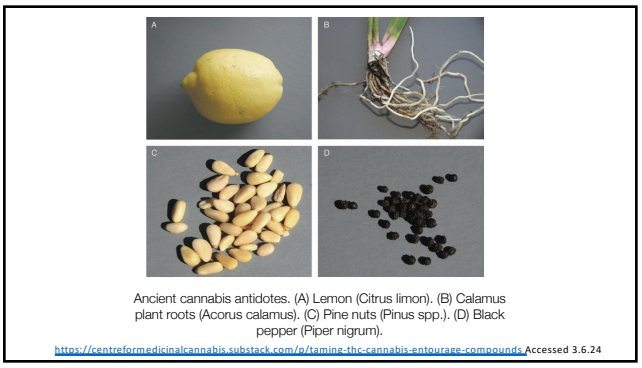

Ancient cannabis antidotes. (A) Lemon (Citrus limon). (B) Calamus plant roots (Acorus calamus). (C) Pine nuts (Pinus spp.). (D) Black pepper (Piper nigrum).

https://centreformedicinalcannabis.substack.com/p/taming-thc-cannabis-entourage-compounds Accessed 3.6.24

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Where can you get educated about cannabis?

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University of British Columbia
Toronto Metropolitan University
McGill University
Okanagan College
Niagara College
Durham College
Loyalist College
Seneca College
Kwantlen Polytechnic University
Coast Mountain College
Mount Royal University
Norquest College
Cannabis Training University

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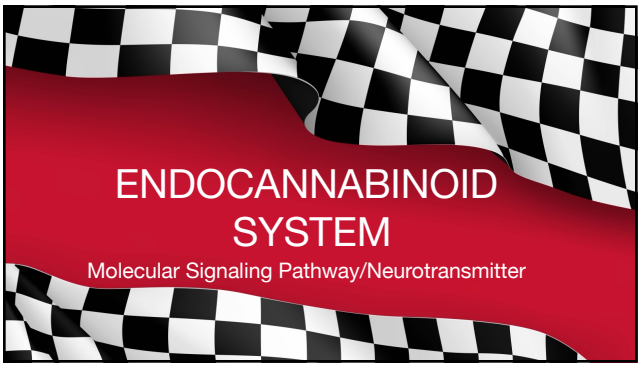

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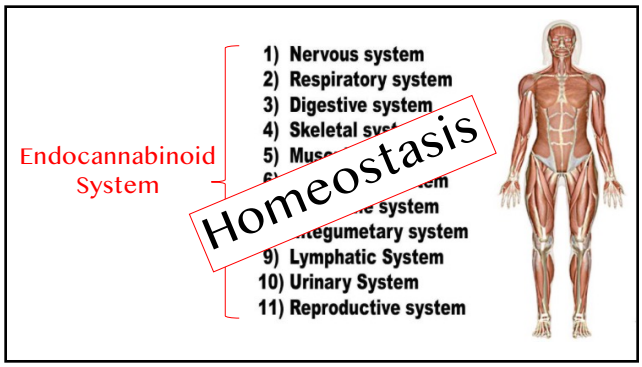

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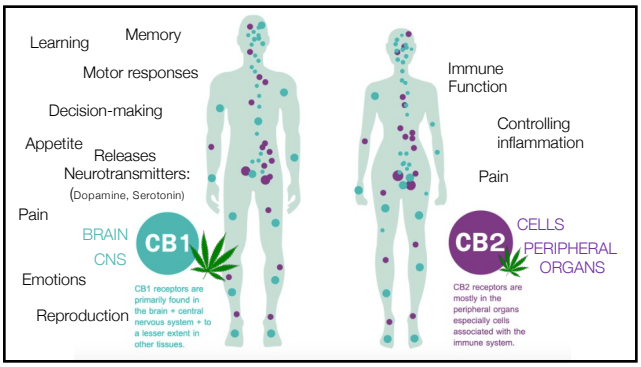

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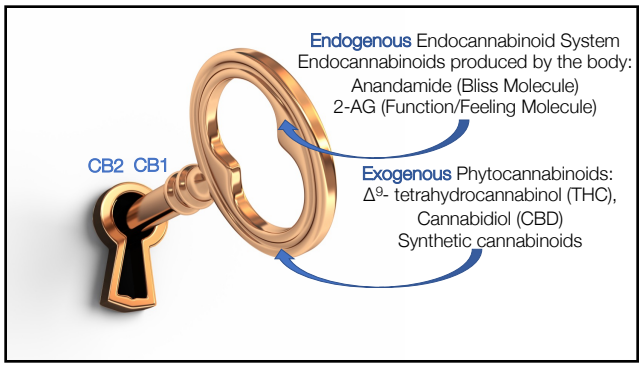

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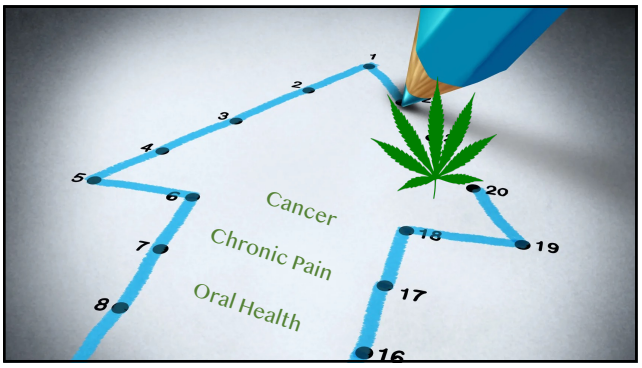

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Cannabis use during pregnancy and postpartum

Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician. 2020 Feb;66(2):98-103. PMID: 32060189; PMCID: PMC7021337.

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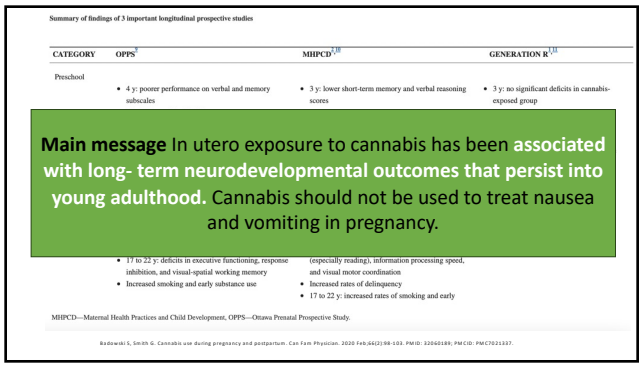
Summary of findings of 3 important longitudinal prospective studies

CATEGORY	OPPS[9]	MHPCD[7,10]	GENERATION R[11]
Preschool	• 4 y: poorer performance on verbal and memory subscales	• 3 y: lower short-term memory and verbal reasoning scores	• 3 y: no significant deficits in cannabis-exposed group
	• 17 to 22 y: deficits in executive functioning, response inhibition, and visual-spatial working memory • Increased smoking and early substance use	(especially reading), information processing speed, and visual motor coordination • Increased rates of delinquency • 17 to 22 y: increased rates of smoking and early	

Main message In utero exposure to cannabis has been **associated with long- term neurodevelopmental outcomes that persist into young adulthood.** Cannabis should not be used to treat nausea and vomiting in pregnancy.

MHPCD—Maternal Health Practices and Child Development, OPPS—Ottawa Prenatal Prospective Study.

Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician. 2020 Feb;66(2):98-103. PMID: 32060189; PMCID: PMC7021337.

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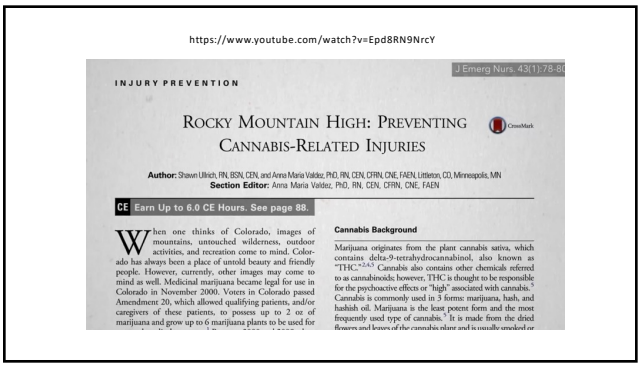
https://www.youtube.com/watch?v=Epd8RN9NrcY

INJURY PREVENTION

ROCKY MOUNTAIN HIGH: PREVENTING CANNABIS-RELATED INJURIES

Author: Shawn Ulrich, RN, BSN, CEN, and Anna Maria Valdez, PhD, RN, CEN, CFRN, CNE, FAEN, Littleton, CO, Minneapolis, MN
Section Editor: Anna Maria Valdez, PhD, RN, CEN, CFRN, CNE, FAEN

CE Earn Up to 6.0 CE Hours. See page 88.

Cannabis Background

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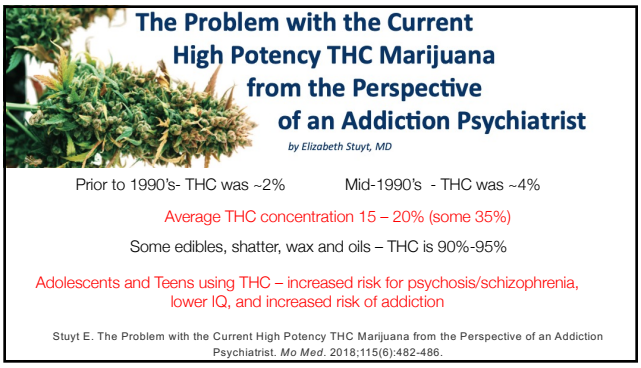

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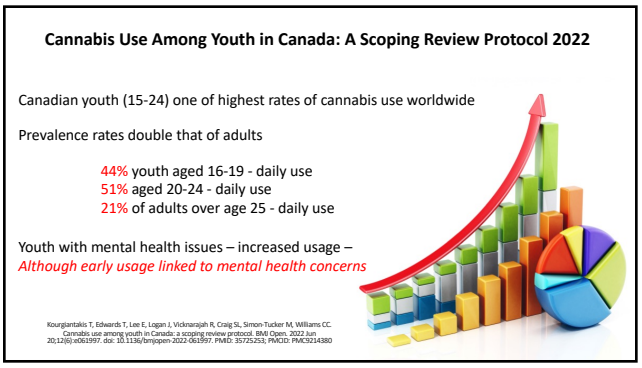

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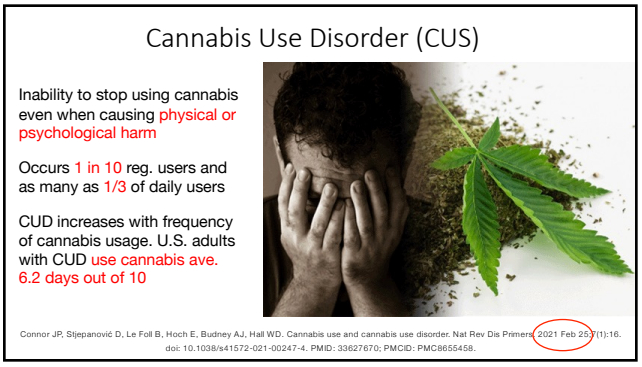

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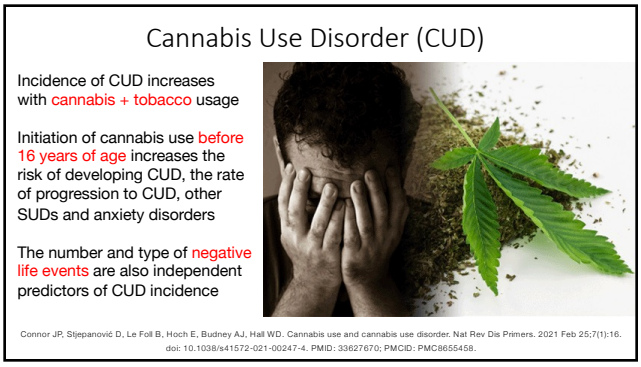

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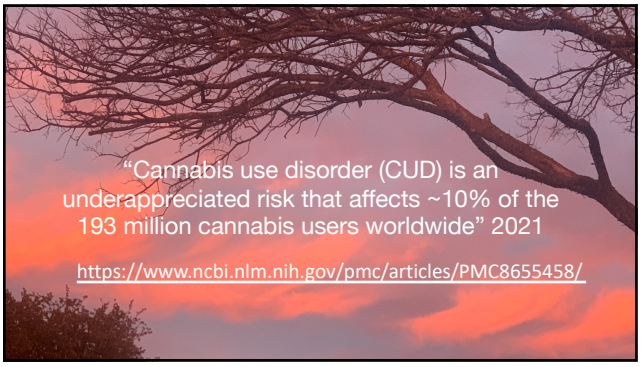

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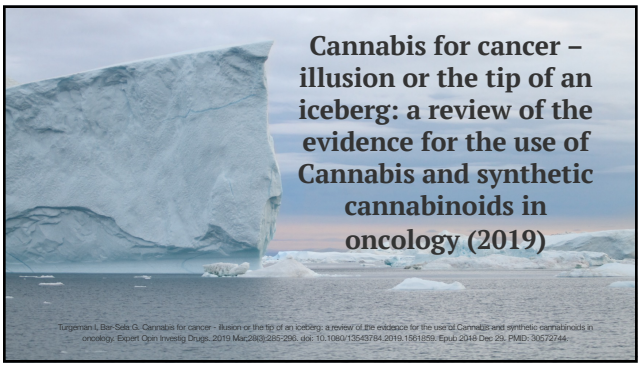

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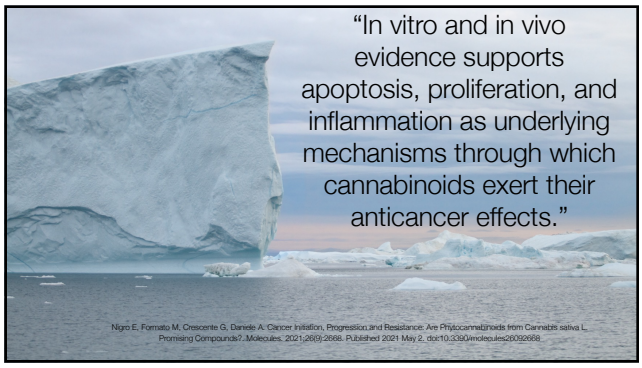

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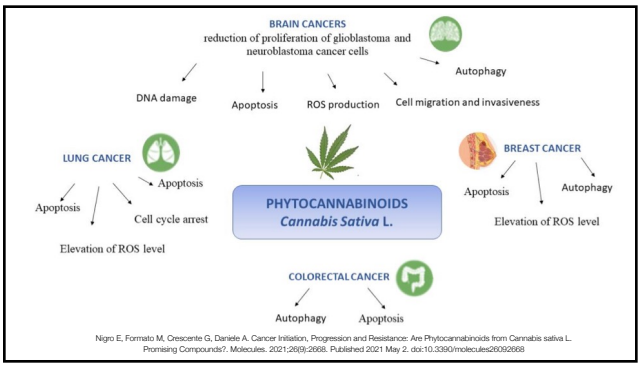

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Anti-cancer effects of cannabinoids and endocannabionoid receptors

Messenger to transfer hormones & adrenaline	cAMP	•Inhibit breast cancer cell migration (CBDA. Takeda et al. 2012)
Involved in cell growth, proliferation & survival	MAPK	•Decrease gastric cancer cell viability and proliferation (Pagano et al. 2017) •Induce apoptosis in leukemia, lymphoma cells (THC. Liu et al. 2008)
Involved in apoptosis & cell proliferation	Akt	•Induce apoptosis, anti-proliferation, anti-angiogenic, anti-invasive effects in breast cancer cells (Caffarel et al. 2010) •Inhibit *in vitro* chemotaxis, chemoinvasion and *in vivo* tumor growth, lung metastasis (Preet et al. 2011)
Regulates cell proliferation & apoptosis	Ceramide	•Prostate cancer cell death by (AEA and CB_2 agonist Mimeault et al. 2003) •Induce apoptosis in pancreatic cells via CB_2R (Carracedo et al. 2006) •Blocking ceramide prevents agonist induced inhibition of glioma cell growth (Carracedo et al. 2006)

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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Drug interactions

(Drug Enhancement with Cannabis)

- Increase potency of chemotherapy in leukemia cells (Scott et al. 2017)
- Synergistic inhibition of pancreas cell growth with gemcitabine (Donadelli et al. 2011)
- Enhance paclitaxel pro-apoptotic effect in gastric cancer cells (AEA. Miyato et al. 2009)
- Potentiate vinblastine cytotoxicity (THC and CBD. Holland et al. 2006)
- Enhance efficacy of irradiation in murine glioma (Scott et al. 2014)

Cannabis in Glioblastoma Studies

Phase 1

Intracranial THC in GBM: decreased biomarker expression (Guzman et al. 2006)

Phase 2

THC/CBD with TMZ in GBM: Safety, survival advantage (ABSTRACT. Twelves et al. 2017)

A peer-reviewed article has not yet been published

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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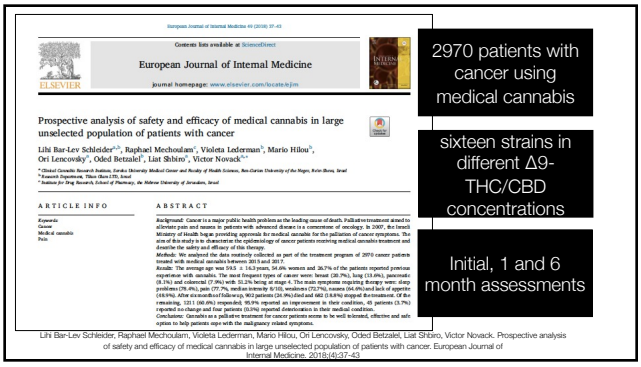

European Journal of Internal Medicine

Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer

Lihi Bar-Lev Schleider[a,*], Raphael Mechoulam[c], Violeta Lederman[b], Mario Hilou[b], Ori Lencovsky[b], Oded Betzalel[b], Liat Shbiro[c], Victor Novack[b,*]

2970 patients with cancer using medical cannabis

sixteen strains in different Δ9-THC/CBD concentrations

Initial, 1 and 6 month assessments

Lihi Bar-Lev Schleider, Raphael Mechoulam, Violeta Lederman, Mario Hilou, Ori Lencovsky, Oded Betzalel, Liat Shbiro, Victor Novack. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. European Journal of Internal Medicine. 2018;(4):37-43

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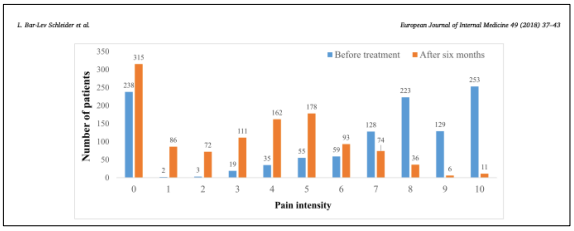

60% success rate (Defined by moderate or significant improvement in patient condition after 6 months of cannabis)

1/3 of patients were able to **reduce other medications**: Analgesics, sedatives, opioids, & corticosteroids

20% reported good QOL at beginning of study. **70% reported good QOL at end of 6 months**

Lihi Bar-Lev Schleider, Raphael Mechoulam, Violeta Lederman, Mario Hilou, Ori Lencovsky, Oded Betzalel, Liat Shbiro, Victor Novack. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. European Journal of Internal Medicine. 2018;(4):37-43

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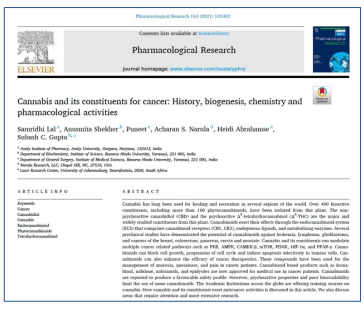

Pharmacological Research

Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities

Samridhi Lal[1], Anoushka Shekher[2], Puneet[2], Acharan S. Narula[3], Heidi Abrahamse[4], Subash C. Gupta[5,*]

Preclinical studies have demonstrated the potential of cannabinoids against: leukemia, lymphoma, glioblastoma, cancers of the breast, colorectum, pancreas, cervix, lung and prostate.

Cannabinoids can block cell growth, progression of cell cycle and induce apoptosis selectively in tumor cells.

Cannabinoids can also enhance the efficacy of cancer therapeutics.

Lal S, Shekher A, Puneet, Narula AS, Abrahamse H, Gupta SC. Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities. Pharmacol Res. 2021 Jan;163:105302. doi: 10.1016/j.phrs.2020.105302. Epub 2020 Nov 24. PMID: 33246167.

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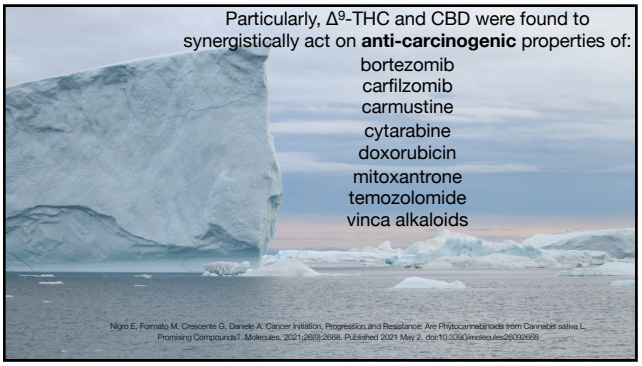

Particularly, Δ⁹-THC and CBD were found to synergistically act on **anti-carcinogenic** properties of:

bortezomib
carfilzomib
carmustine
cytarabine
doxorubicin
mitoxantrone
temozolomide
vinca alkaloids

Nigro E, Formato M, Crescente G, Daniele A. Cancer Initiation, Progression, and Resistance: Are Phytocannabinoids from Cannabis sativa L. Promising Compounds?. Molecules. 2021;26(9):2668. Published 2021 May 2. doi:10.3390/molecules26092668

80

Table 1. Anti-cancer effects of cannabinoids in various cancer cell lines.

Cancer Type	Model/Cell Line	Compound	Effective Dose	Effects	References
Breast	MCF-7	Cannabidiol (CBD)	8.2 μM/2.6 mg/L	Inhibition of cancer cell growth and proliferation	[13]
		CBD-rich extract (~70% CBD)	6.0 μM/2.7 mg/L		
		Δ^9-tetrahydrocannabinol (Δ^9-THC)	14.2 μM/4.5 mg/L		
		AEA	1.4 μM/0.5 mg/L		[53]
	MDA-MB-231	CBD	2.2 μM/0.7 mg/L	Inhibition of cancer cell growth, induction of apoptosis	[54]
		WIN-55,212-2, JWH-133	10 μM/4.3 mg/L, 10 μM/3.1 mg/L	Inhibition of proliferation	[55]
	Xenograft-MBA-MD-231 cells	CBD	5 mg/kg (i.p.)	Reduced tumour size and volume	[13]
		CBD-rich extract (~70% CBD)	6.5 mg/kg (i.p.)		
		WIN-55,212-2, JWH-133	5 mg/kg (i.p.)	Reduced tumour growth, angiogenesis and metastasis	[55]
Cervical	SiHa	CBD	3.2 μg/mL/3.2 mg/L	Inhibition of cancer cell growth, induction of apoptosis	[46]
	HeLa		3.2 μg/mL/3.2 mg/L		
	ME-180		1.5 μg/mL/1.5 mg/L		
Colon	HCT8	CB-13	>50 nmol/L/0.02 mg/L	Inhibition of cancer cell growth	[49]
	SW480				
	HCA7				
	HCT15				
	HCT-116	CBG	≥3.0 μM/0.9 mg/L	Reduced viability of cancer cells	[56]
	Xenograft-HCT-116	CBG	3 and 10 mg/kg (i.p.)	Inhibition of tumour growth	

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Table 1. *Cont.*

Cancer Type	Model/Cell Line	Compound	Effective Dose	Effects	References
Glioma	U251	CBD	0.6 μM/0.2 mg/L	Inhibition of cancer cell growth	[47]
		Δ^9-THC	3.3 μM/1 mg/L		
	U87	CBD	0.6 μM/0.2 mg/L		
		Δ^9-THC	3.3 μM/1 mg/L		
	GSC3832	CBD	3.5 μM/1.1 mg/L	Inhibition of viability	[57]
	GSC387	CBD	2.6 μM/0.8 mg/L		
	U87MG	CBD	>25 μM/>7.9 mg/L	Reduced viability and induce cancer cell death	[58]
	Xenograft-U87	CBD	6.7 mg with 75 mg micro-particles	Inhibition of tumour growth	[59]
Multiple Myeloma	U266	CBD	32.2 μM/10.1 mg/L	Reduced cancer cell viability, increased cytotoxicity, inhibition of cancer cell migration	[60,61]
		Δ^9-THC	39.5 μM/12.4 mg/L		
		CBD + Δ^9-THC + carfilzomib	(0–50 μM/0–15.7 mg/L) CBD + (12.5–50 μM/3.9–15.7 mg/L) Δ^9-THC + (12.5–100 nM/0.009–0.072 mg/L) carfilzomib		
	$U266_{TRPV2}$	CBD	19.8 μM/6.2 mg/L		
	RPMI	CBD	22.4 μM/7.0 mg/L		
		Δ^9-THC	30.8 μM/9.7 mg/L		
		CBD + Δ^9-THC + carfilzomib	(0–50 μM/0–15.7 mg/L) CBD + (12.5–50 μM/3.9–15.7 mg/L) Δ^9-THC + (0.9–7.5 nM/0.0006–0.005 mg/L) carfilzomib		
	$RPMI_{TRPV2}$	CBD	13.5 μM/4.2 mg/L		

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Activity of phytocannabinoids and endocannabinoids in preclinical cancer model.

Phytocannabinoid

Δ^9 -THC

- Selectively inhibited the growth of melanoma cell lines over normal melanocytes [98]; induced hypo… Rb protein, cell-cycle arrest…
- Inhibited RhoA-FAK-S…
- Increased … lines […
- Reve…
- CEM…
- Ex…
- In …
- …
- Induced …
- Reduced the proliferat… induced by 17β-estradiol […
- Induced apoptosis in MiaPaCa2 and Panc-1 … cell lines through ER stress [118].
- Induced cell cycle arrest by inducing G2-M arrest and down-regulating Cdc2 in breast cancer cells [120].
- Reduced cell growth and induced apoptosis in prostate cancer cells [121,122].

Cannabidiol

- Downregulated Id-1 gene expression, glioma cell invasion and self-renewal [100].
- Increased radiosensitivity and induced apoptosis in glioma cell lines [101].
- Reduced survival of glioma stem cells by augmenting levels of ROS [102].
- Exhibited antiproliferative activities in glioma cell lines [102].
- Reversed multidrug resistance in T lymphoblastoid leukaemia … line [104].
- …ptosis in murine lymphoma (EL-4) and the human … and Jurkat) cell lines [105].
- … A549 and H460 lung cancer cell lines by … ion of PPARγ and COX-2 [108].
- …on lung and cervical cancer cell line … ion of TIMP-1 [109].
- …A549 lung cancer cells by … ersion of PAI-1 [110].
- …duced apoptosis in human breast … ed invasion and metastasis in … [112].
- … chemotaxis in SUM159 cell line by … ng [113].
- … expression and suppressed cell prolifer… …n in MDA-MB231 cell line [114].
- … cell growth in mice model bearing MDA-MB-231 … east cancer cell line [115].
- Induced apoptosis in HeLa and ME-18 cervical cancer cell lines [119].
- Induced apoptosis and suppressed proliferation in SGC-7901 gastric cancer cell line by increasing ROS production and inducing cell-cycle arrest [90].
- Induced apoptosis and reduced cell proliferation in prostate cancer cells [121,122].

Future studies on cannabis should be focused more on the dosage, drug combination and route of administration. This will generate solid evidence for the use of this molecule in cancer patients.

Lal S, Shekhar A, Puneet, Narula AS, Abrahamse H, Gupta SC. Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities. Pharmacol Res. 2021 Jan;163:105302. doi: 10.1016/j.phrs.2020.105302. Epub 2020 Nov 24. PMID: 33246167.

83

Conflicting reports...

Hart et al. demonstrated that while high concentrations of cannabinoids have antiproliferative effects on tumors, treatment of lung, brain and genitourinary carcinoma cell lines with low concentrations results in rapid epidermal growth factor receptor and metalloprotease-dependent cancer cell proliferation

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

84

In a multi-variant model, the authors found significantly reduced response rate to immunotherapy in a cohort of 140 patients with, and without cannabionoid treatment, after taking into account confounders such as performance status and Cannabis composition.

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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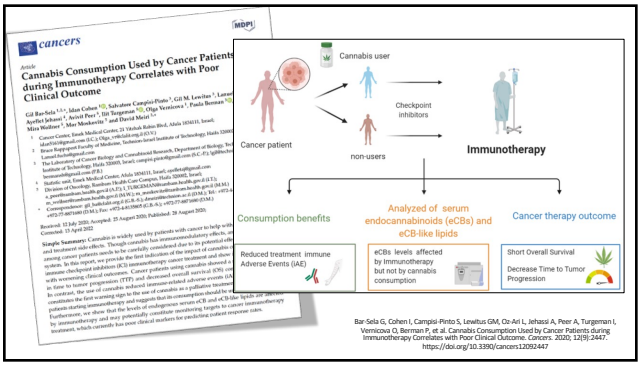

Bar-Sela G, Cohen I, Campisi-Pinto S, Lewitus GM, Oz-Ari L, Jehassi A, Peer A, Turgeman I, Vernicova O, Berman P, et al. Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome. *Cancers*. 2020; 12(9):2447. https://doi.org/10.3390/cancers12092447

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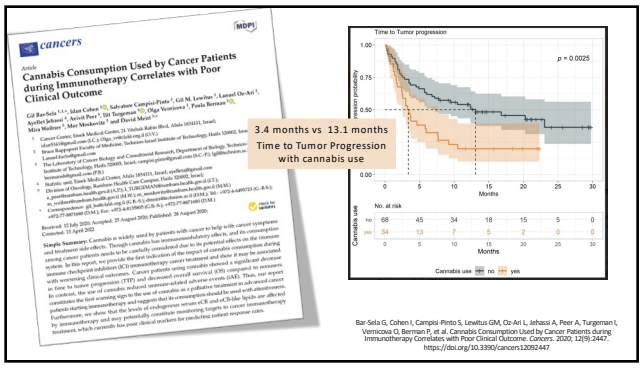

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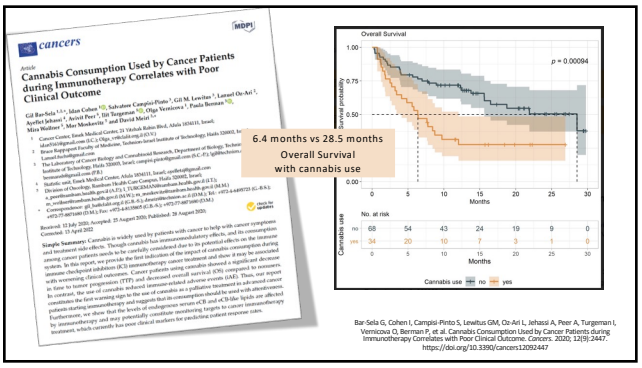

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Published in Australia in 2020
141 Scientific References
Peer Reviewed

Pre-clinical studies show Δ9-tetrahydrocannabinol (THC) inhibits growth & proliferation of cancer cells through modulation of CB1 & CB2 receptors, but clinical data is lacking.

In spite of demonstrated anti-cancer properties of Δ9-THC, this cannabinoid has also been revealed to promote tumor growth, invasion and metastasis in some cancer cell types and THC usage can reduce effectiveness of immune checkpoint inhibitors.

89

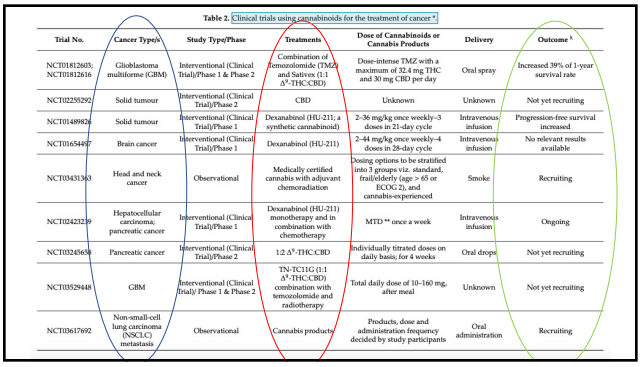

Table 2. Clinical trials using cannabinoids for the treatment of cancer *

Trial No.	Cancer Type/s	Study Type/Phase	Treatments	Dose of Cannabinoids or Cannabis Products	Delivery	Outcome ^
NCT01812603; NCT01812616	Glioblastoma multiforme (GBM)	Interventional (Clinical Trial)/Phase 1 & Phase 2	Combination of Temozolomide (TMZ) and Sativex (1:1 Δ⁹-THC:CBD)	Dose-intense TMZ with a maximum of 32.4 mg THC and 30 mg CBD per day	Oral spray	Increased 39% of 1-year survival rate
NCT02255292	Solid tumour	Interventional (Clinical Trial)/Phase 2	CBD	Unknown	Unknown	Not yet recruiting
NCT01489826	Solid tumour	Interventional (Clinical Trial)/Phase 1	Dexanabinol (HU-211; a synthetic cannabinoid)	2–36 mg/kg once weekly–3 doses in 21-day cycle	Intravenous infusion	Progression-free survival increased
NCT01654497	Brain cancer	Interventional (Clinical Trial)/Phase 1	Dexanabinol (HU-211)	2–44 mg/kg once weekly–4 doses in 28-day cycle	Intravenous infusion	No relevant results available
NCT03431363	Head and neck cancer	Observational	Medically certified cannabis with adjuvant chemoradiation	Dosing options to be stratified into 3 groups viz. standard, frail/elderly (age > 65 or ECOG 2), and cannabis-experienced	Smoke	Recruiting
NCT02423239	Hepatocellular carcinoma; pancreatic cancer	Interventional (Clinical Trial)/Phase 1	Dexanabinol (HU-211) monotherapy and in combination with chemotherapy	MTD ** once a week	Intravenous infusion	Ongoing
NCT03245636	Pancreatic cancer	Interventional (Clinical Trial)/Phase 2	1:2 Δ⁹-THC:CBD	Individually titrated doses on daily basis; for 4 weeks	Oral drops	Not yet recruiting
NCT03529448	GBM	Interventional (Clinical Trial)/ Phase 1 & Phase 2	TN-TC11G (1:1 Δ⁹-THC:CBD) combination with temozolomide and radiotherapy	Total daily dose of 10–160 mg, after meal	Unknown	Not yet recruiting
NCT03617692	Non-small-cell lung carcinoma (NSCLC) metastasis	Observational	Cannabis products	Products, dose and administration frequency decided by study participants	Oral administration	Recruiting

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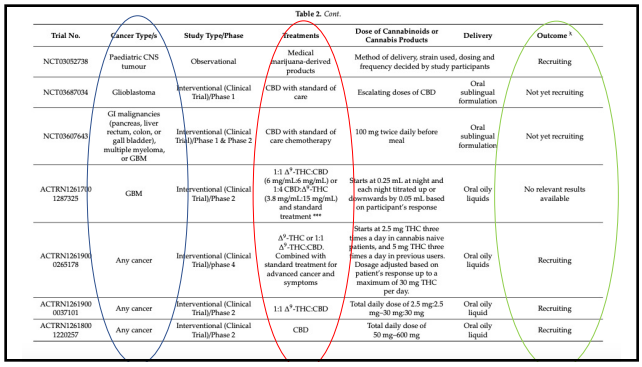

Table 2. Cont.

Trial No.	Cancer Type/s	Study Type/Phase	Treatments	Dose of Cannabinoids or Cannabis Products	Delivery	Outcome ^
NCT03052738	Paediatric CNS tumour	Observational	Medical marijuana-derived products	Method of delivery, strain used, dosing and frequency decided by study participants		Recruiting
NCT03687034	Glioblastoma	Interventional (Clinical Trial)/Phase 1	CBD with standard of care	Escalating doses of CBD	Oral sublingual formulation	Not yet recruiting
NCT03607643	GI malignancies (pancreas, liver rectum, colon, or gall bladder), multiple myeloma, or GBM	Interventional (Clinical Trial)/Phase 1 & Phase 2	CBD with standard of care chemotherapy	100 mg twice daily before meal	Oral sublingual formulation	Not yet recruiting
ACTRN1261700 1287325	GBM	Interventional (Clinical Trial)/Phase 2	1:1 Δ⁹-THC:CBD (6 mg/mL:6 mg/mL) or 1:4 CBD:Δ⁹-THC (3.8 mg/mL:15 mg/mL) and standard treatment ***	Starts at 0.25 mL at night and each night titrated up or downwards by 0.05 mL based on participant's response	Oral oily liquids	No relevant results available
ACTRN1261900 0265178	Any cancer	Interventional (Clinical Trial)/phase 4	Δ⁹-THC or 1:1 Δ⁹-THC:CBD. Combined with standard treatment for advanced cancer and symptoms	Starts at 2.5 mg THC three times a day in cannabis naive patients, and 5 mg THC three times a day in previous users. Dosage adjusted based on patient's response up to a maximum of 30 mg THC per day.	Oral oily liquids	Recruiting
ACTRN1261900 0037101	Any cancer	Interventional (Clinical Trial)/Phase 2	1:1 Δ⁹-THC:CBD	Total daily dose of 2.5 mg:2.5 mg–30 mg:30 mg	Oral oily liquid	Recruiting
ACTRN1261800 1220257	Any cancer	Interventional (Clinical Trial)/Phase 2	CBD	Total daily dose of 50 mg–600 mg	Oral oily liquid	Recruiting

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Ongoing Clinical Trials

- THC, CBD combinations
- THC, CBD independent or combined with chemotherapies
- THC, CBD independent or combined with radiotherapies
- THC, CBD independent or combined with immunotherapies

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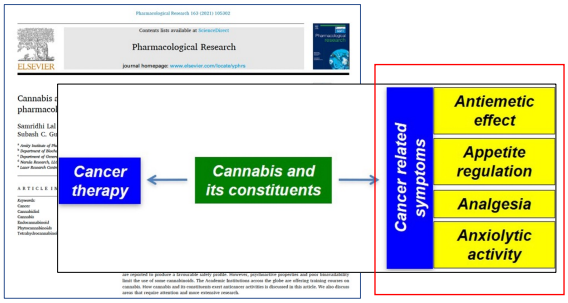

Lal S, Shekher A, Puneet, Narula AS, Abrahamse H, Gupta SC. Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities. Pharmacol Res. 2021 Jan;163:105302. doi: 10.1016/j.phrs.2020.105302. Epub 2020 Nov 24. PMID: 33246167.

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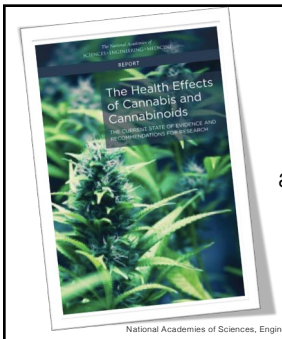

There is conclusive or substantial evidence that cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)

National Academies of Sciences, Engineering, and Medicine 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

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Cannabis Indications in Oncology

Strong Evidence - green | Weak Evidence - yellow | No significant evidence - red

Chemotherapy induced nausea and vomiting	Cancer associated pain	Anorexia and cachexia syndrome
Insomnia	Depression and anxiety	Cancer treatment

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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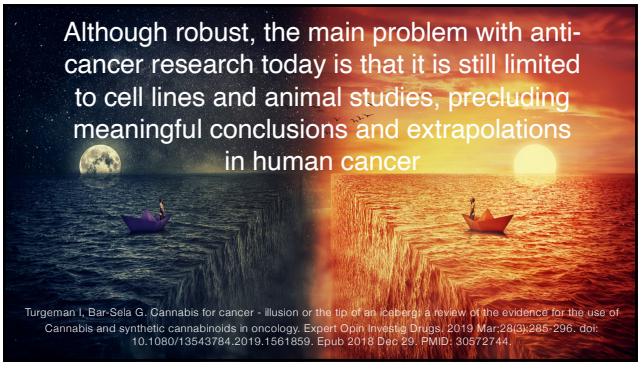

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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Integrative Therapies in Cancer Care: An Update on the Guidelines May 31, 2024

American Society of Clinical Oncology and the Society for Integrative Oncology have collaborated to develop guidelines for the application of integrative approaches in the management of anxiety, depression, fatigue and use of cannabinoids and cannabis in patients with cancer

Clinicians should recommend against using cannabis or cannabinoids as a cancer-directed treatment unless within the context of a clinical trial...evidence remains insufficient...with exception to augment an antiemetic regimen

Gowin K, Muminovic M, Zick SM, Lee RT, Lacchetti C, Mehta A. Integrative Therapies in Cancer Care: An Update on the Guidelines. Am Soc Clin Oncol Educ Book. 2024 Jun;44(3):e431554. doi: 10.1200/EDBK_431554. PMID: 38820485.

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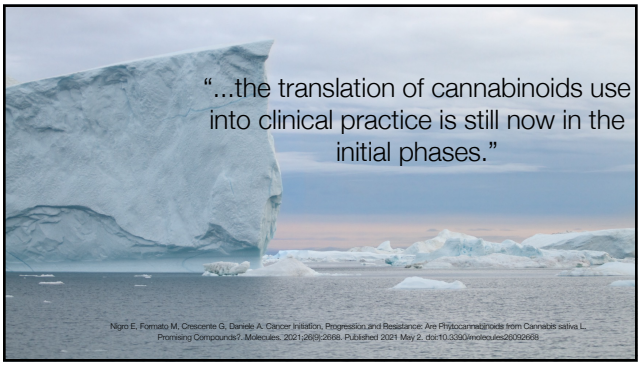

Nigro E, Formato M, Crescente G, Daniele A. Cancer Initiation, Progression and Resistance: Are Phytocannabinoids from Cannabis sativa L. Promising Compounds?. Molecules. 2021;26(9):2668. Published 2021 May 2. doi:10.3390/molecules26092668

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According to a 2003 study in the Journal of Cannabis Therapeutics 80% palliative care patients were comfortable with the use of cannabis for pain management

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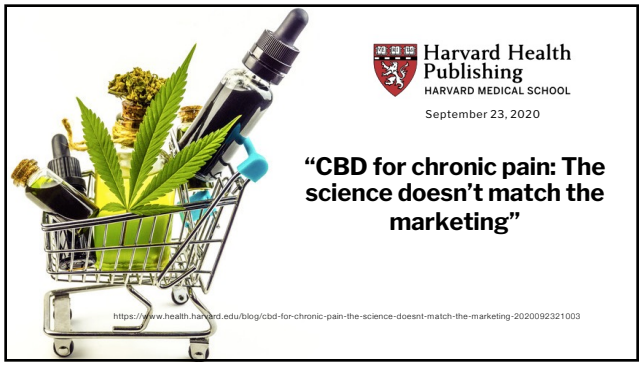

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Mariiuana strains to relieve pain

•**ACDC:**This is a non-psychoactive strain that makes you feel happy, uplifted, relaxed and focused. HIGH THC/HIGH CBD

•**Blackberry Kush:** High in THC, Blackberry Kush is particularly known for its intense pain-relieving effects. It also makes you feel relaxed, sleepy and euphoric and is best taken at nighttime or on days you don't have much to do

.

•**Harlequin:** HIGH CBD/LOW THC. Due to its CBD and THC content, Harlequin kills your pain while keeping you mentally alert. As such, this is a good option for daytime use.

https://www.marijuanadoctors.com/conditions/cancer/

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Current Pain and Headache Reports (2023) 27:57–63
https://doi.org/10.1007/s11916-023-01101-w

ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Medical Cannabis for Chronic Nonmalignant Pain Management

Maha Hameed[1] · Sakshi Prasad[1] · Esha Jain[1] · Bekir Nihat Dogrul[1] · Ahmad Al-Oleimat[1] · B
Selia Chowdhury[1] · Edzel Lorraine Co[1] · Saloni Mitra[1] · Jonathan Quinonez[2] · Samir Ruxm

Accepted: 23 January 2023 / Published online: 10 March 2023

Abstract
Purpose of Review Cannabis has been used since ancient times for medical and recreational
will document the validity of how medical cannabis can be utilized for chronic nonmalignant
Recent Findings Current cannabis research has shown that medical cannabis is indicated for sy
conditions not limited to cancer, chronic pain, headaches, migraines, and psychological disorde
stress disorder). Δ9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are active ingredients in
a patient's symptoms. These compounds work to decrease nociception and symptom frequency via the
system. Research regarding pain management is limited within the USA as the Drug Enforcement Agency
it as a schedule one drug. Few studies have found a limited relationship between chronic pain and medical
Summary A total of 77 articles were selected after a thorough screening process using PubMed and Goog
paper demonstrates that medical cannabis use provides adequate pain management. Patients suffering from
lignant pain may benefit from medical cannabis due to its convenience and efficacy.

Hameed M, Prasad S, Jain E, Dogrul BN, Al-Oleimat A, Pokhrel B, Chowdhury S, Co EL, Mitra S, Quinonez J, Ruxmohan S, Stein J. Medical Cannabis for Chronic Nonmalignant Pain Management. Curr Pain Headache Rep. 2023 Apr;27(4):57-63. doi: 10.1007/s11916-023-01101-w. Epub 2023 Mar 10. PMID: 36897501; PMCID: PMC9999073.

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Take Aways…

> 60% of medical licenses issued for use of medicinal cannabis are for chronic pain (2017)

CB1 receptors can decrease neurotransmitters thereby reducing pain
CB2 receptors can reduce inflammation pain and alter release of pro-inflammatory cytokines

Most patients surveyed use more than one form of cannabis and most surveyed use combinations of Indica and Sativa

Majority preferred balanced THC:CBD ratios or high CBD ratios; only a minority preferred high THC ratios

Many but not all studies show a reduction in opioids when using cannabis for pain mgmt

Hameed M, Prasad S, Jain E, Dogrul BN, Al-Oleimat A, Pokhrel B, Chowdhury S, Co EL, Mitra S, Quinonez J, Ruxmohan S, Stein J. Medical Cannabis for Chronic Nonmalignant Pain Management. Curr Pain Headache Rep. 2023 Apr;27(4):57-63. doi: 10.1007/s11916-023-01101-w. Epub 2023 Mar 10. PMID: 36897501; PMCID: PMC9999073.

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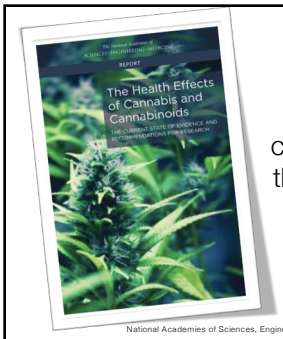

There is conclusive or substantial evidence that cannabinoids are effective for the treatment of chronic pain in adults (cannabis).

National Academies of Sciences, Engineering, and Medicine 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

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Medical Cannabis Reduces Chronic or Neuropathic Pain in Advanced Cancer Patients (2017)

Review 1975-2017: 5 Clinical studies evaluating effect of THC or CBD on controlling cancer pain
- THC oil capsules
- THC:CBD oromucosal spray
- THC oromucosal spray

Doses 2.7 – 42.2 mg/day THC and 0-40 mg CBD daily

Higher THC correlated in increased pain relief in some studies
1 Study found sig. pain relief in low doses: 1.7 – 10.8 mg THC in combination 2.5 – 10 mg CBD

Blake A, Wan BA, Malek L, DeAngelis C, Diaz P, Lao N, Chow E, O'Hearn S. A selective review of medical cannabis in cancer pain management. Ann Palliat Med 2017;6(Suppl 2):S215-S222. doi: 10.21037/apm.2017.08.05

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Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies (2018)

104 studies were eligible (9958 participants)

Studies that showed 30% reduction in pain were: 29.0% (cannabinoids) vs 25.9% (placebo)

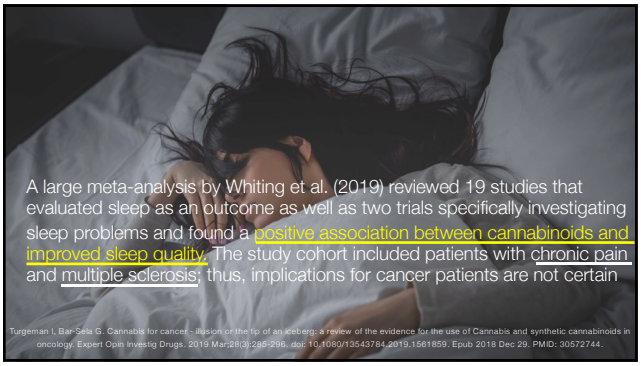
For 50% reduction in pain, outcomes were 18.2% (cannabinoids) vs 14.4% (placebo)

Pooled change in pain intensity with cannabis/cannabinoids was equivalent to a 3 mm reduction on a 100 mm visual analogue scale greater than placebo groups

Evidence for effectiveness of cannabinoids in CNCP is limited

Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018 Oct;159(10):1932-1954. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469.

109



A large meta-analysis by Whiting et al. (2019) reviewed 19 studies that evaluated sleep as an outcome as well as two trials specifically investigating sleep problems and found a positive association between cannabinoids and improved sleep quality. The study cohort included patients with chronic pain and multiple sclerosis; thus, implications for cancer patients are not certain

Turgeman I, Bar-Sela G. Cannabis for cancer - illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology. Expert Opin Investig Drugs. 2019 Mar;28(3):285-296. doi: 10.1080/13543784.2019.1561859. Epub 2018 Dec 29. PMID: 30572744.

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Medicinal Cannabis for Inflammatory Bowel Disease: A Survey of Perspectives, Experiences, and Current Use in Australian Patients (2020)

Online survey IBD patients / 838 responses

Results showed 25.3% (n = 212) respondents were current or previous users of MC (18.1%

Only 3 respondents reported using legally assessed products

Usage: smoking (joints 34.2%; water pipe/bongs 14.5%) or oral liquid (19.7%)

IBD symptoms reported as positively affected by cannabis included abdominal pain, stress, sleep, cramping, and anxiety. Most users (92.7%) endorsed cannabis as effective in symptom management.

Melissa J Benson, PhD, Sarah V Abeley, BSc, Susan J Connor, MD, PhD, Crispin J Corte, MD, PhD, Lewis J Martin, PhD, Lucy K Gold, BSc, Anastasia S Suraev, MPsych(Clin), Iain S McGregor, PhD, Medicinal Cannabis for Inflammatory Bowel Disease: A Survey of Perspectives, Experiences, and Current Use in Australian Patients, Crohn's & Colitis 360, Volume 2, Issue 2, April 2020, otaa015, https://doi.org/10.1093/crocol/otaa015

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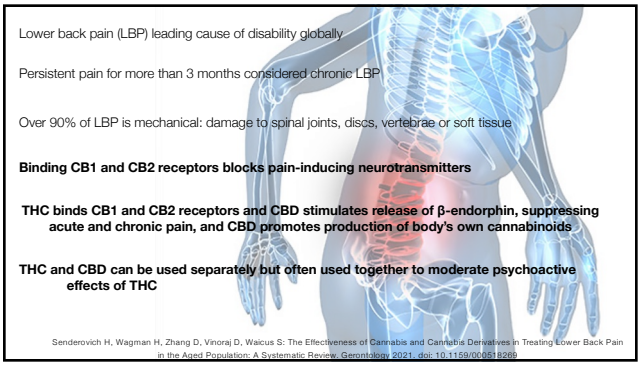

Lower back pain (LBP) leading cause of disability globally

Persistent pain for more than 3 months considered chronic LBP

Over 90% of LBP is mechanical: damage to spinal joints, discs, vertebrae or soft tissue

Binding CB1 and CB2 receptors blocks pain-inducing neurotransmitters

THC binds CB1 and CB2 receptors and CBD stimulates release of β-endorphin, suppressing acute and chronic pain, and CBD promotes production of body's own cannabinoids

THC and CBD can be used separately but often used together to moderate psychoactive effects of THC

Senderovich H, Wagman H, Zhang D, Vinoraj D, Waicus S: The Effectiveness of Cannabis and Cannabis Derivatives in Treating Lower Back Pain in the Aged Population: A Systematic Review. Gerontology 2021. doi: 10.1159/000518269

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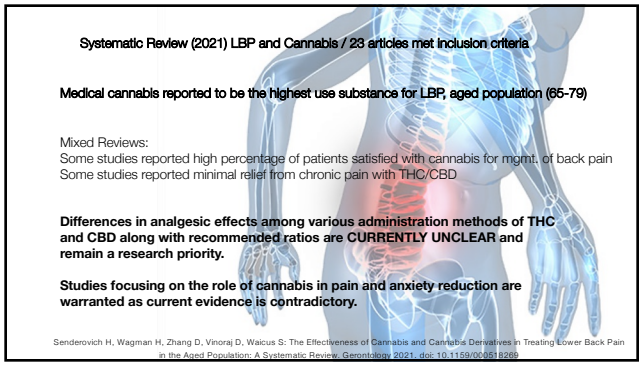

Systematic Review (2021) LBP and Cannabis / 23 articles met inclusion criteria

Medical cannabis reported to be the highest use substance for LBP, aged population (65-79)

Mixed Reviews:
Some studies reported high percentage of patients satisfied with cannabis for mgmt. of back pain
Some studies reported minimal relief from chronic pain with THC/CBD

Differences in analgesic effects among various administration methods of THC and CBD along with recommended ratios are CURRENTLY UNCLEAR and remain a research priority.

Studies focusing on the role of cannabis in pain and anxiety reduction are warranted as current evidence is contradictory.

Senderovich H, Wagman H, Zhang D, Vinoraj D, Waicus S: The Effectiveness of Cannabis and Cannabis Derivatives in Treating Lower Back Pain in the Aged Population: A Systematic Review. Gerontology 2021. doi: 10.1159/000518269

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Cannabis-Based Medicines and Medical Cannabis for Chronic Neuropathic Pain (2021)

Key Points

Current systematic reviews on cannabis-based medicines and medical cannabis for chronic neuropathic pain come to divergent conclusions on efficacy.

Physicians who decide to use cannabis-based medicines or medical cannabis must be mindful of the limited sound evidence for effect and concerns for harms.

"After reading this paper, readers are invited to formulate their own conclusions regarding the potential benefits and harms of cannabis-based medicines and medical cannabis for the treatment of chronic neuropathic pain."

Petzke F, Tölle T, Fitzcharles MA, Häuser W. Cannabis-Based Medicines and Medical Cannabis for Chronic Neuropathic Pain. CNS Drugs. 2022 Jan;36(1):31-44. doi: 10.1007/s40263-021-00879-w. Epub 2021 Nov 21. PMID: 34802112; PMCID: PMC8732831

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Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline (2021)

Expert guideline panel comprised of physicians, patients & methodologists

4 systematic reviews analyzing benefits versus harms

"The guideline expert panel issued a weak recommendation to offer a trial of non-inhaled medical cannabis or cannabinoids, in addition to standard care and management (if not sufficient), for people living with chronic cancer or non-cancer pain."

Busse JW, Vankrunkelsven P, Zeng L, Heen AF, Merglen A, Campbell F, Granan LP, Aertgeerts B, Buchbinder R, Eom M, Jaunlink D, Samer C, Siemieniuk RAC, Kumar N, Cooper L, Brown J, Izcovich L, Zeraatkar D, Wang L, Guyatt GH, Vandvik PO, Agoritsas T. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ. 2021 Sep 8;374:n2040. doi: 10.1136/bmj.n2040. PMID: 34497062.

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Medical Cannabis-Based Products for Chronic Pain: A Systematic Review (2022)

18 RCT & 7 Cohort Studies
Duration: 1-6 months
56% Enrolled experienced neuropathic pain
3-89% females, per study

Synthetic products with High THC:CBD ratio (>98%THC) = moderate improvement in pain severity (increased risk for sedation and dizziness)

Sublingual sprays with comparable THC:CBD ratio (1.1:1) = small improvement in pain severity (increased risk for sedation, dizziness and nausea)

McDonagh MS, Morasco BJ, Wagner J, Ahmed AY, Fu R, Kansagara D, Chou R. Cannabis-Based Products for Chronic Pain : A Systematic Review. Ann Intern Med. 2022 Aug;175(8):1143-1153. doi: 10.7326/M21-4520. Epub 2022 Jun 7. PMID: 35667066.

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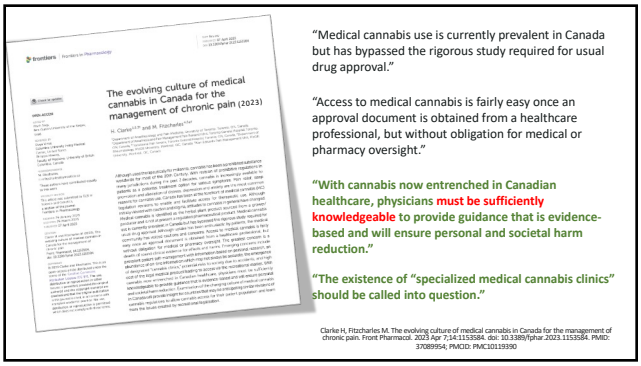

"Medical cannabis use is currently prevalent in Canada but has bypassed the rigorous study required for usual drug approval."

"Access to medical cannabis is fairly easy once an approval document is obtained from a healthcare professional, but without obligation for medical or pharmacy oversight."

"With cannabis now entrenched in Canadian healthcare, physicians must be sufficiently knowledgeable to provide guidance that is evidence-based and will ensure personal and societal harm reduction."

"The existence of "specialized medical cannabis clinics" should be called into question."

Clarke H, Fitzcharles M. The evolving culture of medical cannabis in Canada for the management of chronic pain. Front Pharmacol. 2023 Apr 7;14:1153584. doi: 10.3389/fphar.2023.1153584. PMID: 37089954; PMCID: PMC10119390

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Expert Consensus-Based Recommendations on Dosing

Table 1 Global task force on medical cannabis dosing and administration for treatment of chronic pain

Last name	First name	Specialty	Country
Bell	Alan	Family Medicine	Canada
Bhaskar	Arun	Pain Medicine	United Kingdom
Brown	Matthew	Pain Medicine	United Kingdom
Clarke	Hance	Anesthesiology	Canada
Cyr	Claude	Family Medicine	Canada
Eisenberg	Elon	Neurology and Pain Medicine	Israel
Ferreira	Ricardo	Pain Medicine	Brazil
Frohlich	Eva	Anesthesiology and Pain Management	South Africa
Georgius	Peter	Pain Medicine	Australia
Hogg	Malcolm	Pain Medicine	Australia
Horsted	Tina	Pain Medicine	Denmark
MacCallum	Caroline	Internal Medicine	Canada
Moulin	Dwight	Pain Medicine	Canada
Müller-Vahl	Kirsten	General Psychiatry, Neurology	Germany
O'Connell	Colleen	Physical Medicine, Rehabilitation	Canada
Sealey	Robert	Family Medicine	Canada
Seiboldt	Marc	Anesthesiology, Pain and Addiction Medicine	Germany
Shiota	Aaron	Primary Care Pharmacy	Canada
Sulak	Dustin	Osteopathic Medicine	United States
Vigano	Antonio	Palliative Medicine	Canada

Bhaskar, A., Bell, A., Boivin, M. *et al.* Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res* **3**, 22 (2021). https://doi.org/10.1186/s42238-021-00073-1

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Routine protocol for medical cannabis dosing and administration

From: Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process

Starting cannabinoid type	CBD-predominant
Starting CBD dose	CBD-predominant 5 mg twice daily
CBD titration	↑ CBD-predominant 10 mg/day (total daily dose) every 2 to 3 days
When to add THC	If patient is not reaching treatments goals when CBD-predominant dose is ≥ 40 mg/day
Starting THC dose	2.5 mg/day
THC titration	↑ 2.5 mg every 2-7 days until goals are met or a maximum dose of 40 mg/day THC is reached*

*Refer for expert consultation if considering > 40 mg/day THC

Bhaskar, A., Bell, A., Boivin, M. *et al.* Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res* **3**, 22 (2021). https://doi.org/10.1186/s42238-021-00073-1

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Conservative protocol for medical cannabis dosing and administration

From: Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process

Starting cannabinoid type	CBD-predominant
Starting CBD dose	CBD-predominant 5 mg once or twice daily
CBD titration	↑ CBD-predominant 5- 10 mg/day (total daily dose) every 2 to 3 days
When to add THC	If patient is not reaching treatments goals when CBD-predominant dose is ≥ 40 mg/day
Starting THC dose	1 mg/day
THC titration	↑ 1 mg every 7 days until treatment goals are met or a maximum dose of 40 mg/day THC is reached*

*Refer for expert consultation if considering > 40 mg/day THC

Bhaskar, A., Bell, A., Boivin, M. *et al.* Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res* **3**, 22 (2021). https://doi.org/10.1186/s42238-021-00073-1

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Rapid Protocol for Urgent Pain Management, Palliative Care, or Heavy Cannabis Users

From: Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process

Starting cannabinoid type	Balanced THC:CBD
Starting dose	2.5-5.0 mg of each cannabinoid once or twice daily
Titration amount	↑ 2.5-5 mg every 2-3 days of each cannabinoid once or twice daily until goals are met or a maximum dose of 40 mg/day THC is reached*

*Refer for expert consultation if considering > 40 mg/day THC

Bhaskar, A., Bell, A., Boivin, M. *et al.* Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res* **3**, 22 (2021). https://doi.org/10.1186/s42238-021-00073-1

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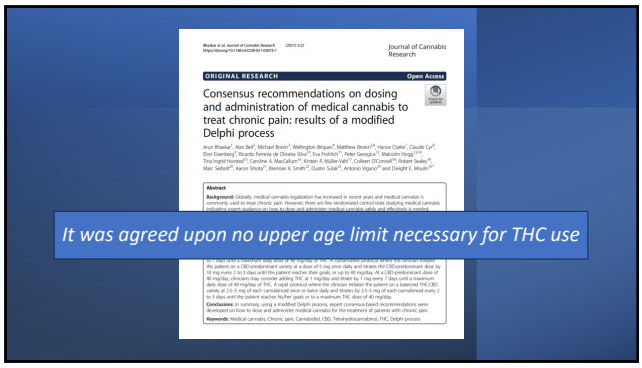

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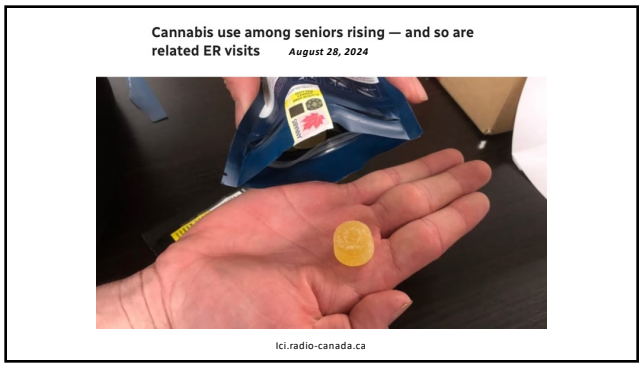

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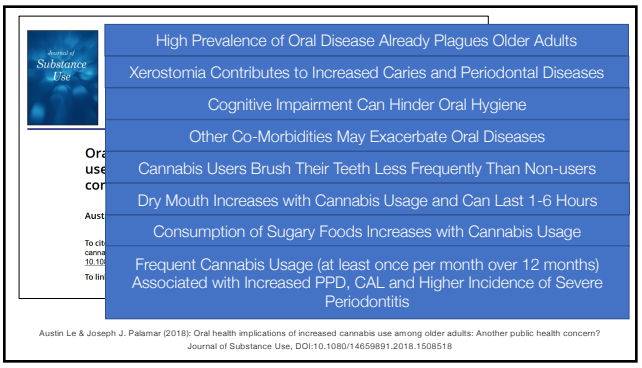

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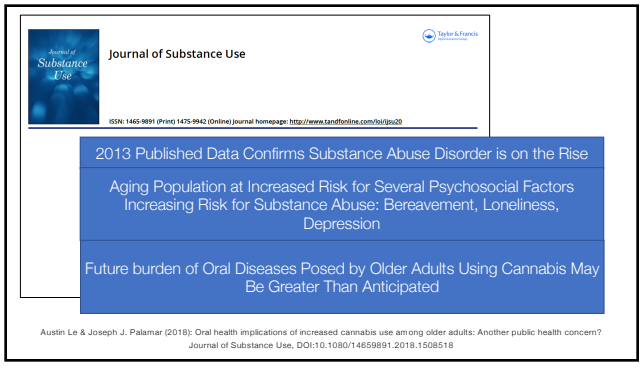

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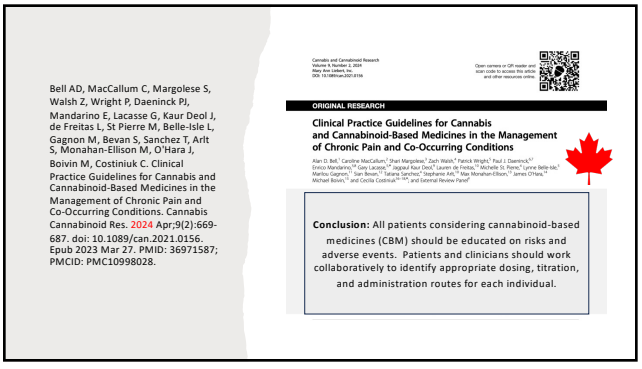

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Take Aways...

70 studies included / 19 Systematic Reviews

14/19 reviews reported cannabinoids provided analgesia at least in some contexts, however in some Instances analgesic effect was "moderate" or "small"

Adverse events, while common, were mostly mild: dizziness, drowsiness, dry mouth

Strong recommendation with good quality evidence for CBM to be used as a monotherapy or adjunctive Therapy for people living with chronic pain

Oral CBM may be preferred over inhaled products due to longer duration (6-8hrs)

Oil and capsule formulas easier for accurate dosing - titration recommended

THC formulations had strongest results for pain reduction compared to other CBM

Bell AD, MacCallum C, Margolese S, Walsh Z, Wright P, Daeninck PJ, Mandarino E, Lacasse G, Kaur Deol J, de Freitas L, St Pierre M, Belle-Isle L, Gagnon M, Bevan S, Sanchez T, Arit S, Monahan-Ellicon M, O'Hara J, Boivin M, Costiniuk C. Clinical Practice Guidelines for Cannabis and Cannabinoid-Based Medicines in the Management of Chronic Pain and Co-Occurring Conditions. Cannabis Cannabinoid Res. 2024 Apr;9(2):669-687. doi: 10.1089/can.2021.0156. Epub 2023 Mar 27. PMID: 36971587; PMCID: PMC10998028.

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Rx Interactions with Cannabis

Immunosuppressant: Tacrolimus/CBD only
Blood Thinner: Clopidogrel, Warfarin
Anti-fungal, Ketoconazole
Bronchodilator: Theophylline
Antibiotic: Sulphamethoxazole
Anti-seizure: Clobazam
Anti-seizure: Valproate
Alcohol

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Cannabis & Oral Health

Is it possible the anti-inflammatory properties of cannabis offset negative consequences in the oral cavity?

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Oral health

In a statewide survey of California dentists and dental hygienists, only 1 in 4 reported asking patients about cannabis, in contrast to the approximately 60% who asked specifically about tobacco cigarettes.

Chaffee BW, Urata J, Couch ET, Silverstein S. Dental professionals' engagement in tobacco, electronic cigarette and cannabis patient counseling. JDR Clin Trans Res 2020April;5(2):133–145. doi: 10.1177/2380084419861384. Epub 2019 Jul 19.

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Open Access Review

The Current and Potential Application of Medicinal Cannabis Products in Dentistry

by Henry Lowe [1,2,3,4], Ngeh Toyang [2,3], Blair Steele [1,*], Joseph Bryant [1], Wilfred Ngwa [5,6] and Kaveh Nedamat [7,8]

1 Biotech R & D Institute, University of the West Indies, Mona 99999, Jamaica
2 Vilotos Pharmaceuticals Inc., Baltimore, MD 21202, USA
3 Flavocure Biotech Inc., Baltimore, MD 21202, USA
4 Department of Medicine, University of Maryland Medical School, Baltimore, MD 21202, USA
5 Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA
6 School of Medicine, Johns Hopkins University, Baltimore, MD 21218, USA
7 Sloan School of Management, Massachusetts Institute of Technology, Cambridge, MA 02142, USA
8 Auraleaf Innovations, Toronto, ON M9B 4H6, Canada
* Author to whom correspondence should be addressed.

Academic Editors: Claude Jaquiéry, Patrick R. Schmidlin and Luca Testarelli

Dent. J. **2021**, 9(9), 106; https://doi.org/10.3390/dj9090106

Chaffee BW, Urata J, Couch ET, Silverstein S. Dental professionals' engagement in tobacco, electronic cigarette and cannabis patient counseling. JDR Clin Trans Res 2020April;5(2):133–145. doi: 10.1177/2380084419861384. Epub 2019 Jul 19.

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"Of particular interest is the potential for the existence of synergistic ratios between cannabinoids which when combined, can produce optimal anti-bacterial, anti-inflammatory, antioxidant and analgesic effects.

One example is between CBD and CBG where studies on neuroinflammation, a key factor in amyotrophic lateral sclerosis (ALS) show that, when combined, their benefits are enhanced."

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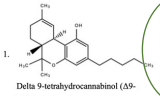
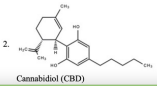
Chemical Structures of Major Secondary Metabolites of *Cannabis sativa* L.	Significant Properties	References
Major cannabinoids		
1.  Delta 9-tetrahydrocannabinol (Δ9-THC)	Anti-microbial Anti-inflammatory Analgesic Antioxidant Anti-cancer Anti-tumor	[84,98,99,100,101,102,103,104,105]
2.  Cannabidiol (CBD)	Anti-microbial Anti-inflammatory Analgesic Anti-cancer Anti-metastatic Antioxidant Analgesic	[35,84,98,99,100,101,102,103,106,107,108,109,110]

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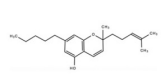
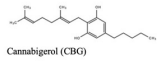
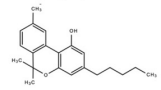
3.	 Cannabichromene (CBC)	Anti-microbial Antibacterial and Anti-fungal Analgesic Anti-nociceptive Antioxidant Anti-inflammatory Anti-depressant	[84,111,112,113,114,115,116]
4.	 Cannabigerol (CBG)	Anti-microbial Analgesic Antioxidant	[84,117,118,119]
5.	 Cannabinol (CBN)	Anti-microbial Analgesic Antioxidant	[84,120,121]

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Potential Applications of Secondary Metabolites of *C. sativa* L. in Dentistry	Appropriate Property of Secondary Metabolite	Reference
Cannabinoids		
1. General oral hygiene (Cannabidiol, delta9-tetrahydrocannabinol ajulemic acid, Cannabigerol)	Antifungal Antibacterial	[41,84,93,105,117,118,210]
2. Toothache (Cannabidiol, HU-320)	Analgesic	[41,151,163]
3. Dental caries/cavities (Cannabidiol, Cannabigerol and Delta9-tetrahydrocannabinol)	Anti-bacterial Analgesic	[41,47,48,84,93,117,118,191,211]
4. Abscesses (Cannabidiol and delta9-tetrahydrocannabinol)	Anti-bacterial Anti-pruritic	[191]
5. Prevention of biofilm attachment on teeth (Cannabidiol and delta9-tetrahydrocannabinol)	Anti-bacterial	[84,191]
6. Burning Mouth Syndrome (Cannabidiol)	Analgesic	[191]
7. Oral and Salivary Gland Cancers (Cannabidiol)	Anti-cancer Anti-metastatic	[191]

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Potential Applications of secondary metabolites of *C. sativa* L. in dentistry.

8.	Periodontitis (most severe form of gum disease) (Cannabidiol, HU-320, delta9-tetrahydrocannabinol, AEA)	Anti-bacterial Anti-inflammatory Analgesic	[84,151,188,191,212,213]
9.	Periodontal (Gum) disease (Cannabidiol, delta9-tetrahydrocannabinol, Cannabigerol and HU-320)	Anti-bacterial Anti-inflammatory Analgesic	[84,93,117,118,151,211]
10.	Gingivitis (Cannabidiol, delta9-tetrahydrocannabinol, Cannabigerol, and HU-320)	Anti-bacterial Anti-inflammatory Analgesic	[84,93,117,118,151,211]
11.	Oral Mucositis and other forms of oral cancer (Cannabidiol, delta9-tetrahydrocannabinol, JWH-133m, WIN-55,212-2, Cannabinol, Cannabicyclol)	Anti-bacterial Anti-cancer Anti-metastatic Anti-inflammatory Analgesic Antioxidant	[84,154,191,192,198,214]
12.	Dental Anxiety (Cannabidiol)	Anxiolytic	[191,215]
13.	Sleep issues resulting from dental anxiety (Cannabidiol and delta-9-tetrahydrocannabinol (THC))	Relaxant	[216]

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Promising Potential

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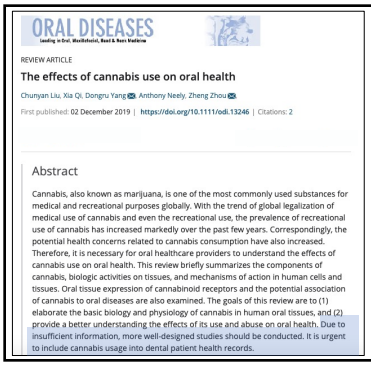

ORAL DISEASES

REVIEW ARTICLE

The effects of cannabis use on oral health

Chunyan Liu, Xia Qi, Dongru Yang, Anthony Neely, Zheng Zhou

First published: 02 December 2019 | https://doi.org/10.1111/odi.13246 | Citations: 2

Abstract

Cannabis, also known as marijuana, is one of the most commonly used substances for medical and recreational purposes globally. With the trend of global legalization of medical use of cannabis and even the recreational use, the prevalence of recreational use of cannabis has increased markedly over the past few years. Correspondingly, the potential health concerns related to cannabis consumption have also increased. Therefore, it is necessary for oral healthcare providers to understand the effects of cannabis use on oral health. This review briefly summarizes the components of cannabis, biologic activities on tissues, and mechanisms of action in human cells and tissues. Oral tissue expression of cannabinoid receptors and the potential association of cannabis to oral diseases are also examined. The goals of this review are to (1) elaborate the basic biology and physiology of cannabis in human oral tissues, and (2) provide a better understanding the effects of its use and abuse on oral health. Due to insufficient information, more well-designed studies should be conducted. It is urgent to include cannabis usage into dental patient health records.

As the leading method of consuming cannabis, marijuana smoking may pose direct and indirect effects on oral health. The evidence to link cannabis use and oral dental diseases is limited and often contradictory

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Cannabis: A joint problem for patients and the dental profession

Table 2 The difference between tobacco and cannabis

Cannabis joints are usually smoked for a longer period of time than tobacco.[4]
Cannabis joints are usually smoked to a shorter joint length, which results in a greater number of toxins entering the mouth.[4]
Cannabis has a higher combustion temperature compared to tobacco.[4]
There is greater carboxyhaemoglobin concentration and tar retention in lower airway in cannabis smokers.[4]
Tobacco found in cigarettes is regulated. Whereas, cannabis is a non-regulated substance.
Tobacco is usually smoked more frequently than cannabis due to the shorter half life of nicotine.[4]

Joshi, S., Ashley, M. Cannabis: A joint problem for patients and the dental profession. *Br Dent J* **220,** 597–601 (2016). https://doi.org/10.1038/sj.bdj.2016.416 [4]Gates P, Jaffe A, Copeland J. Cannabis smoking and respiratory health: Consideration of the literature. *Respirology* 2014; **3:** 655–662.

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Cannabis: A joint problem for patients and the dental profession

22-year-old patient who smoked six cannabis 'joints' a day for the last 8 years.
Cannabis users surveyed: 63% who experienced increased hunger post use – favored sweets

Various studies show 2.5 – 6 times higher decay rates in cannabis users compare to non-users

Joshi, S., Ashley, M. Cannabis: A joint problem for patients and the dental profession. *Br Dent J* **220,** 597–601 (2016). https://doi.org/10.1038/sj.bdj.2016.416

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Cannabis: A joint problem for patients and the dental profession

Table 3 A summary of the oral implications of cannabis use

Oral implications of cannabis use	Associated implications
Dry mouth (Xerostomia)– short term	Increased risk of caries. Increased risk of periodontal disease. Increased risk of frictional injuries. Halitosis.
Thermal injury	Hyperkeratinisation due to higher combustion temperature of cannabis.
Leukoedema	Normal variation. Clinically detectable due to multifactorial reasons: genetics, alcohol, tobacco and cannabis use.
Candidal infection	Increased risk of candidal infection – poor oral hygiene/denture hygiene – nutritional deficiency.
Oral cancer	Cannabis contains similar carcinogens to tobacco. Possibility of a link with cannabis use. However more evidence required.

Joshi, S., Ashley, M. Cannabis: A joint problem for patients and the dental profession. *Br Dent J* **220,** 597–601 (2016). https://doi.org/10.1038/sj.bdj.2016.416

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Cannabis: A joint problem for patients and the dental profession

A sample size of 85 participants were used and divided into two groups. The control group were tobacco smokers only and the test group used cannabis and tobacco

The results obtained showed that cannabis users brushed their teeth less frequently than the control group. In addition, the control group visited their dentist more regularly whereas only 21% in the test group visited their dentist annually.

Joshi, S., Ashley, M. Cannabis: A joint problem for patients and the dental profession. *Br Dent J* **220,** 597–601 (2016). https://doi.org/10.1038/sj.bdj.2016.416

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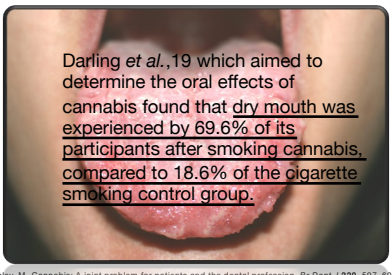
Cannabis: A joint problem for patients and the dental profession



Darling *et al.*,19 which aimed to determine the oral effects of cannabis found that dry mouth was experienced by 69.6% of its participants after smoking cannabis, compared to 18.6% of the cigarette smoking control group.

Joshi, S., Ashley, M. Cannabis: A joint problem for patients and the dental profession. *Br Dent J* **220,** 597–601 (2016). https://doi.org/10.1038/sj.bdj.2016.416

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Cannabis Use and Oral Health in a National Cohort of Adults

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Abstract

Background: Cannabis use is common and increasing among adults. Evidence connects cannabis use to poor periodontal health, but few prospective studies exist of adults in the United States.

Methods: This investigation examined associations between cannabis use and self-reported adverse oral health conditions among participants (N = 18,872) in the Population Assessment of Tobacco and Health (PATH) Study, a nationally representative cohort. Survey-weighted regression modeling estimated associations between cannabis use and seven self-reported measures of oral health status, adjusted for tobacco use and other disease risk factors.

Results: Reporting past-30-days cannabis use in any of PATH Waves 1-3 was positively and statistically significantly associated at Wave 4 with multiple periodontal disease sequelae and with self-rated fair or poor overall oral health (adjusted odds ratio versus never-users: 1.75; 95% confidence interval: 1.52, 2.01).

Conclusions: These findings provide further evidence that cannabis use is an independent risk factor for poor oral health, although study limitations (self-reported outcomes, limited information on cannabis use frequency and modality) must be considered.

Practical implications: Dental professionals should engage patients in clear, nonjudgmental dialogue about cannabis use to address oral health risks and avoid potential patient safety issues in care delivery. General recommendations for addressing cannabis use in dental practice are presented.

18,872 users – self reported outcomes

Cannabis is an independent risk factor for poor oral health, although study limitations *(limited information on cannabis use frequency and modality)* must be considered

Dental professionals should engage patients in non-judgmental dialog about cannabis use

Chaffee BW. Cannabis Use and Oral Health in a National Cohort of Adults. *J Calif Dent Assoc*. 2021;49(8):493-501.

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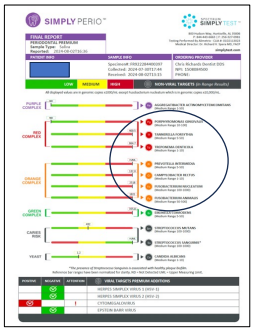
What's your experience?

151

33 yr. old daily cannabis user / 1-2 pre-rolls nightly / 8 years to help manage chronic pain

152



Diagnosis: Generalized gingivitis

Education

GBT therapeutic treatment provided for professional biofilm debridement

Philips Sonicare Power Flosser and Diamond Clean Power Brush for daily biofilm management

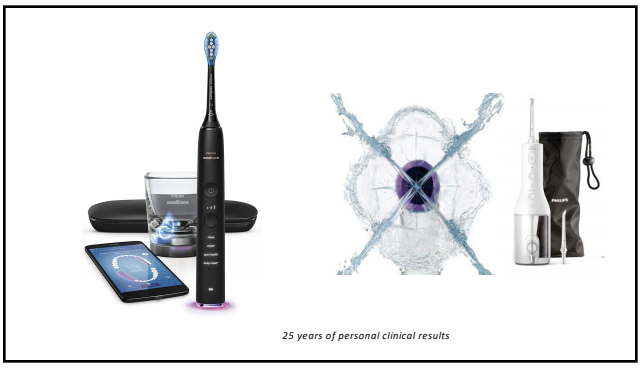
Septodont OraSoothe twice daily swish

Probiora Pro probiotic tablets nightly

Spry mints 5 times daily

153

154



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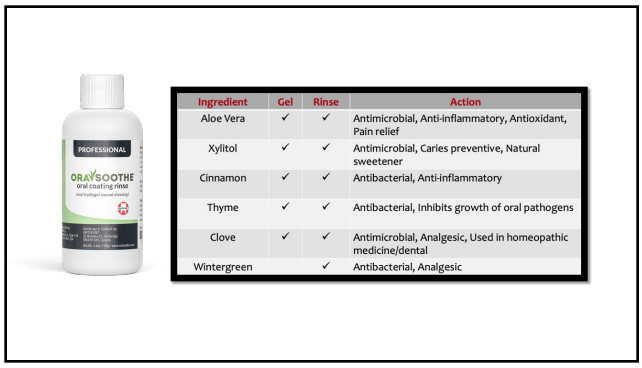

Ingredient	Gel	Rinse	Action
Aloe Vera	✓	✓	Antimicrobial, Anti-inflammatory, Antioxidant, Pain relief
Xylitol	✓	✓	Antimicrobial, Caries preventive, Natural sweetener
Cinnamon	✓	✓	Antibacterial, Anti-inflammatory
Thyme	✓	✓	Antibacterial, Inhibits growth of oral pathogens
Clove	✓	✓	Antimicrobial, Analgesic, Used in homeopathic medicine/dental
Wintergreen		✓	Antibacterial, Analgesic

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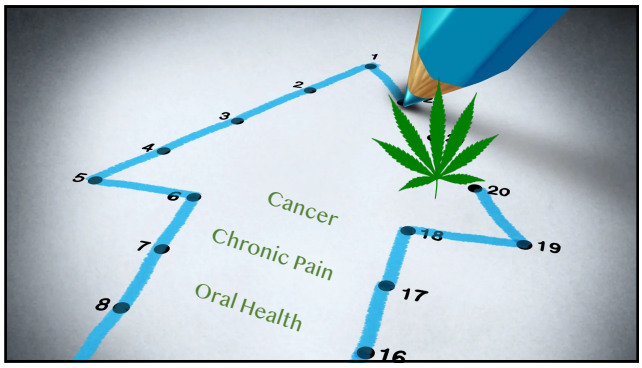

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