

# Cannabinoids 101:

UNDERSTANDING THE SCIENCE OF CANNABIS

CHAPTER 1

# Cannabinoids and cannabis: an overview



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## CHAPTER 1

# Cannabinoids and cannabis:

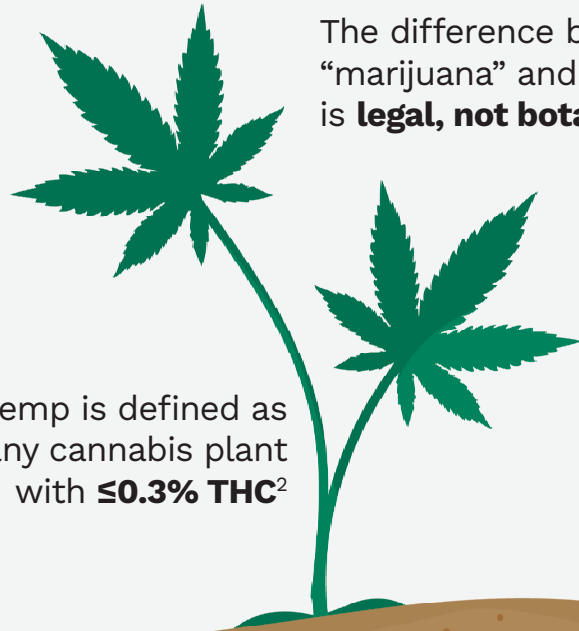


# an overview

# cannabis vs cannabinoids

## ***Cannabis sativa***<sup>1</sup>:

A plant from which specific *cannabinoids* are derived



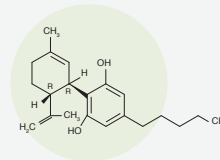
The difference between “marijuana” and “hemp” is **legal, not botanical**<sup>2</sup>

Hemp is defined as any cannabis plant with **≤0.3% THC**<sup>2</sup>

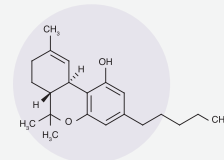
## **Cannabinoids**<sup>1</sup>:

Chemical compounds that can be found in cannabis plants

### **Cannabidiol (CBD)**<sup>3</sup>



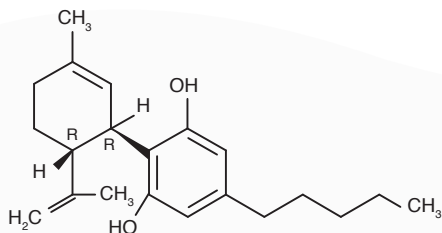
### **Tetrahydrocannabinol (THC)**<sup>1</sup>



### **Others**<sup>1</sup>

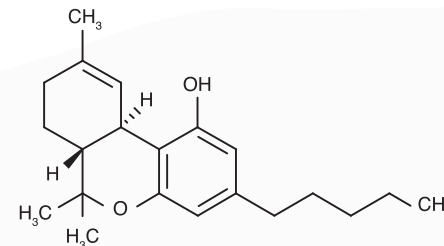
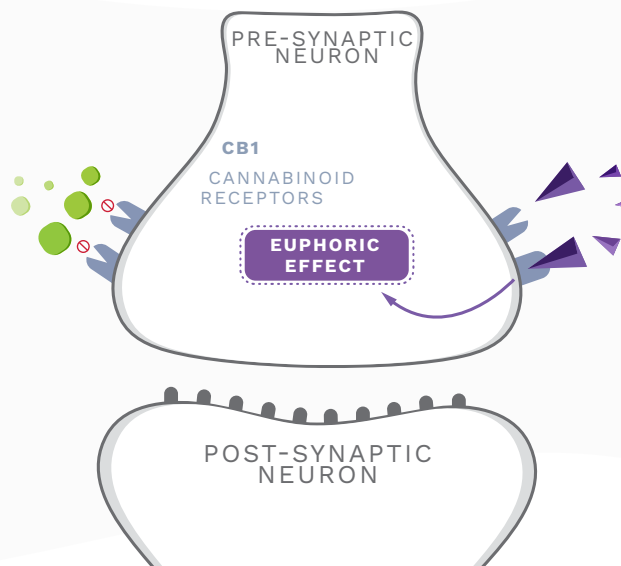
CBG  
CBN  
CBDA  
THCV  
THCA

# CBD and THC are unique compounds<sup>1,3</sup>



## CBD

- Very low affinity for CB1 receptors and **does not cause euphoria**<sup>3,4</sup>
- **Anticonvulsant properties** established in clinical trials<sup>5-7</sup>



## THC

- Affinity for and activity at CB1 receptors; is primarily responsible for marijuana's **euphoric effects**<sup>4,8</sup>

## 3 categories of cannabis-based products



**Pharmaceutical  
formulations**



**Medical marijuana &  
recreational marijuana**



**Hemp**



# pharmaceutical formulations

- Can be plant-derived or synthetic<sup>3,9</sup>
- Studied to evaluate efficacy and safety profile<sup>3,9</sup>
- Controlled preparations that meet FDA standards of consistency and stability<sup>10</sup>



# medical marijuana & recreational marijuana

- Cannabis products that may contain  $>0.3\%$  THC<sup>2</sup>
- Medical and recreational marijuana are defined solely by intended use<sup>2</sup>:
  - **Recreational marijuana:** to induce pleasure, euphoria, relaxation, or enhance sociability<sup>11</sup>
  - **Medical marijuana:** to treat disease or alleviate symptoms by patient choice, in the absence of FDA approval<sup>12</sup>
- Healthcare providers may “recommend” these products but do not prescribe<sup>2</sup>





# hemp

- Defined as  $\leq 0.3\%$  THC<sup>2</sup>
- **<0.3% THC can still cause intoxication<sup>13</sup>**
  - Even 5 mg/day of THC can cause side effects (feeling high, dizziness, confusion, and drowsiness)<sup>9</sup>
  - Can be an **inefficient source of CBD<sup>2</sup>**
- Absorbs heavy metals and chemical waste from soil<sup>2</sup>

## CHAPTER 2

Non–FDA–approved  
cannabis products:



# what we know

# Non-FDA-approved products in the news<sup>14-18</sup>

Pesticides and  
Pot: Lab Results,  
Company Statements

FEBRUARY 22, 2017



Contaminated cannabis  
oil causing emergency  
room visits, NC health  
officials warn

MARCH 06, 2018



Fake CBD Poisoned At  
Least 52 People In Utah  
Last Winter, Officials Say

MAY 26, 2018



Clusters of illness  
linked to CBD  
vapes share second  
connection

OCTOBER 21, 2019



Dangerous Chemicals  
Are Found in Popular  
CBD Products

NOVEMBER 19, 2018



# Cannabis is often grown outdoors<sup>19</sup>

Cannabinoid quality and content can vary depending on<sup>20</sup>:



Hemp is an effective “bioaccumulator” and “phytoremediator,” meaning it **absorbs heavy metals and other chemical waste from the soil<sup>2</sup>**

- The absorption of these heavy metals can impact the quality of the products and the health of those who ingest it<sup>21</sup>

# Many non-FDA-approved CBD products may be **contaminated**<sup>15,18,22</sup>

Some non-FDA-approved  
CBD products have shown  
concentrated amounts of  
**toxic pesticides**<sup>22</sup>



CBD products may be produced using  
**substandard manufacturing** and  
can be contaminated with:



**heavy  
metals**<sup>21</sup>



**mold &  
bacteria**<sup>23,24</sup>



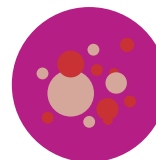
**harmful  
chemicals**<sup>14</sup>

Of **47 states with medical cannabis** laws,  
only **23 have testing requirements**<sup>25,26</sup>



Many exclude “hemp” products  
from testing requirements **completely**<sup>25,26</sup>

Even in state-licensed testing facilities,  
there can be criticisms regarding:



**Lack of testing  
for mold**<sup>23</sup>

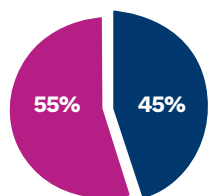


**Technical  
glitches in labs**<sup>23</sup>

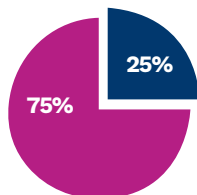


**Inconsistent  
testing methods**<sup>27</sup>

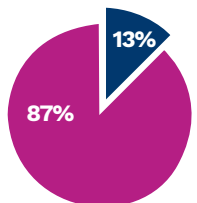
Many non-FDA-approved CBD products may be inaccurately labeled<sup>28</sup>



CBD oil  
(n=40)



CBD tinctures  
(n=20)



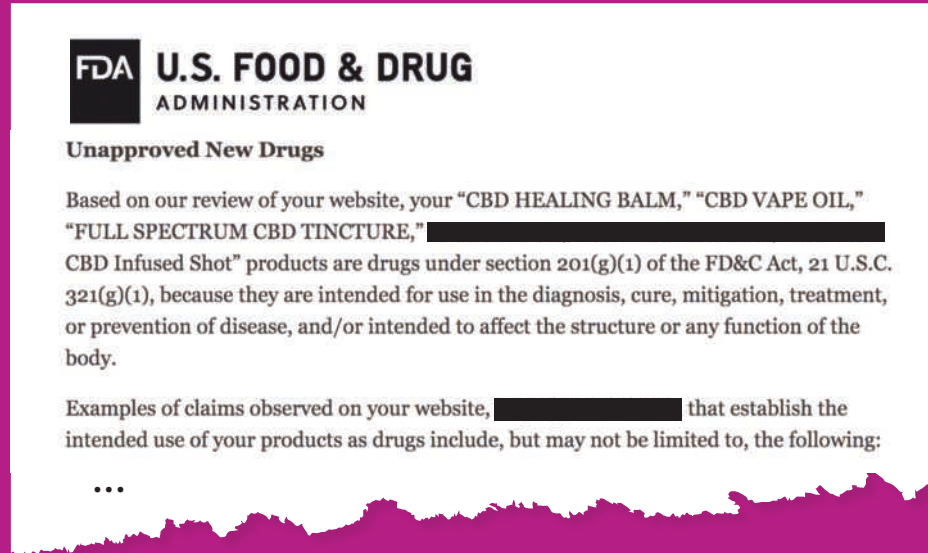
Vaporization liquid  
(n=24)

- Accurate  
(CBD content within 10% of labeled value)
- Inaccurate  
(CBD content more than 10% higher or lower than labeled value)

Of 84 products analyzed, nearly **70%** were inaccurately labeled with respect to CBD and **21.4%** contained THC<sup>28,29</sup>

Due to variable CBD and THC content, the authors concluded that these products should be avoided for pediatric patients<sup>29</sup>

## The FDA warns against **mislabeling and false claims**<sup>30,31</sup>



The FDA continues to send warning letters to non-FDA-approved CBD companies, **noting unsubstantiated medical claims. Their analysis also found mislabeled cannabinoid content**<sup>30</sup>



## **Oversight by healthcare professionals is vitally important**

Cannabinoids can alter the effect of other medications<sup>3</sup>

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Cannabinoids could decrease or increase the levels of other drugs the patient is taking<sup>3</sup>



## CHAPTER 3

What's the  
difference?



# **treating with confidence**

- ✓ FDA-approved
- ✗ Non-FDA-approved



## What's the difference?

# Measured Quality

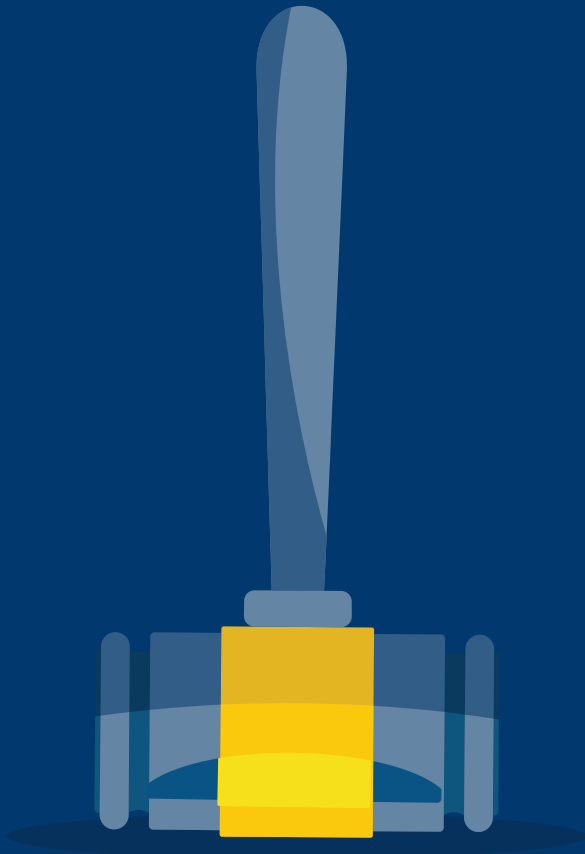
- ✓ Rigorously tested in controlled clinical trials to understand the safety profile and efficacy<sup>3,32</sup>
- ✗ Have not been evaluated in clinical trials for safety; results are anecdotal, relying on parental reporting on patients taking nonstandardized dosing<sup>33-35</sup>
- ✓ Must meet FDA standards for quality and stability<sup>32</sup>
- ✗ Testing standards vary from state to state and lab to lab<sup>27</sup>
- ✓ Consistent concentrations of medicine ensured across every batch<sup>3</sup>
- ✗ Contents may vary between products and batches of the same brand<sup>28</sup>
- ✓ Produced and federally inspected to ensure current good manufacturing practices (cGMP)<sup>32</sup>
- ✗ Unknown inspection of manufacturing sites

- ✓ FDA-approved
- ✗ Non-FDA-approved

## What's the difference?

# Legal Status

- ✓ Federally legal in all 50 states<sup>3</sup>
- ✗ Though federally legal if less than 0.3% THC, products cannot be added to supplements or food products, nor promoted as a medicine<sup>2,36</sup>
- ✓ Available with a prescription
- ✗ Cannot be prescribed, only “recommended”<sup>2</sup>
- ✓ Eligible for insurance coverage
- ✗ Not eligible for insurance coverage
- ✓ Can be legally transported between states
- ✗ Interstate transportation is federally illegal<sup>2</sup>



**References:** 1. ElSohly MA, Gul W. In: *Handbook of Cannabis*. Oxford University Press: United Kingdom. 2014. 2. Mead A. *Epilepsy Behav.* 2017;70(Pt B):288-291. 3. EPIDIOLLEX [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2018. 4. Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. *Neurotherapeutics*. 2015;12(4):747-768. 5. Thiele EA, Marsh ED, French JA, et al. *Lancet*. 2018;391(10125):1085-1096. 6. Devinsky O, Patel AD, Cross JH, et al. *N Engl J Med*. 2018;378(20):1888-1897. 7. Devinsky O, Cross JH, Laux L, et al. *N Engl J Med*. 2017;376(21):2011-2020. 8. Pertwee RG. *Br J Pharmacol*. 2006;147(suppl 1):S163-S171. 9. Marinol [package insert]. North Chicago, IL: AbbVie Inc.; 2017. 10. Food and Drug Administration. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients>. Accessed December 17, 2019. 11. Hall W. In: *Handbook of Cannabis*. Oxford University Press: United Kingdom. 2014. 12. National Institute of Drug Abuse. <https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine>. Accessed December 17, 2019. 13. Vandrey R, Hermann ES, Mitchell JM, et al. *J Anal Toxicol*. 2017;41(2):83-99. 14. NBC Los Angeles. <https://www.nbclosangeles.com/news/pesticide-laced-pot-lab-results-company-statements-i-team/31337/>. Accessed December 17, 2019. 15. The News & Observer. <https://www.newsobserver.com/news/local/article203824334.html>. Accessed December 17, 2019. 16. Forbes. <https://www.forbes.com/sites/janetwburns/2018/05/26/officials-say-fake-cbd-poisoned-at-least-52-people-in-utah-last-winter/#c2f383c7dd3b>. Accessed December 17, 2019. 17. The Denver Post. <https://www.denverpost.com/2019/10/21/cbd-vaping-illness-clusters/>. Accessed December 17, 2019. 18. Consumer Reports. <https://www.consumerreports.org/cbd/dangerous-chemicals-found-in-popular-cbd-products-diamond-cbd-5f-adb/>. Accessed December 17, 2019. 19. Caulkins JP. [https://www.rand.org/content/dam/rand/pubs/working\\_papers/2010/RAND\\_WR764.pdf](https://www.rand.org/content/dam/rand/pubs/working_papers/2010/RAND_WR764.pdf). Accessed December 17, 2019. 20. United Nations Office on Drugs and Crime. [https://www.unodc.org/documents/wdr/WDR\\_2009/WDR2009\\_eng\\_web.pdf](https://www.unodc.org/documents/wdr/WDR_2009/WDR2009_eng_web.pdf). Accessed December 17, 2019. 21. Girdhar M, Sharma NR, Rehman H, et al. *3 Biotech*. 2014;4(6):579-589. 22. Subritzky T, Pettigrew S, Lenton S. *Int J Drug Policy*. 2017;42:86-96. 23. AP News. <https://apnews.com/2cb04323f9074c1ca28001693f6e2a8a/Big-safety-testing-failure-rate-for-California-pot-products>. Accessed December 17, 2019. 24. Thompson GR III, Tuscano JM, Dennis M, et al. *Clin Microbiol Infect*. 2017;23:269-270. 25. GenTech Scientific. <https://cannabis.gentechscientific.com/cannabis-testing-regulation>. Accessed December 17, 2019. 26. Norml. <https://norml.org/laws>. Accessed December 18, 2019. 27. Jikomes N, Zoorob M. *Sci Rep*. 2018;8(1):4519. 28. Bonn-Miller MO, Loflin MJE, Thomas BF, et al. *JAMA*. 318(17):1708-1709. 29. Freedman DA, Patel AD. *Pediatr Neurol Briefs*. 2018;32:3. 30. Food and Drug Administration. <https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products>. Accessed December 17, 2019. 31. Food and Drug Administration. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/koi-cbd-llc-593391-11222019>. Accessed December 17, 2019. 32. Data on file. Greenwich Biosciences, Inc., Carlsbad, CA. 33. Porcari GS, Fu C, Doll ED, et al. *Epilepsy Behav*. 2018;80:240-246. 34. Press CA, Knupp KG, Chapman KE. *Epilepsy Behav*. 2015;45:49-52. 35. Rosenberg EC, Louik J, Conway E, et al. *Epilepsia*. 2017;58(8):e96-e100. 36. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys>. Accessed December 17, 2019.



# CANNABINOIDS 101



## ***Cannabis sativa:***

A plant from which specific cannabinoids (such as THC and CBD) are derived<sup>1</sup>

## **THC and CBD are unique compounds with different effects on the brain**

**CBD** has been shown to reduce seizures in clinical studies and does not cause a “high”<sup>3,4</sup>

**THC** is responsible for the “high” marijuana causes<sup>3,8</sup>

## **3 categories of cannabis-based products**



### **Pharmaceutical formulations<sup>3,9,10</sup>**

- Studied for safety and efficacy
- FDA standards ensure consistency and stability



### **Medical & recreational marijuana<sup>2</sup>**

- Defined by intent of use
- “Recommended” but not prescribed in the absence of FDA approval



### **Hemp<sup>2</sup>**

- No more than 0.3% THC (can be enough to cause intoxication)
- Inefficient source of CBD
- Absorbs heavy metals and chemical waste from soil

## **NON-FDA-APPROVED PRODUCTS**

**Products may be produced with substandard manufacturing and can be contaminated with<sup>14,21,23,24:</sup>**



**Mold & bacteria**



**Heavy metals**



**Harmful chemicals**

**ONLY  
23/47**

states with medical cannabis laws have testing requirements<sup>25,26</sup>

Of 84 products analyzed,  
**~70%**  
**were inaccurately labeled**  
with respect to CBD and

**21.4%**  
**contained THC<sup>28,29</sup>**



The FDA continues to send warning letters, noting **unsubstantiated medical claims and mislabeled cannabinoid content<sup>29</sup>**

## **FDA-APPROVED MEDICINE**



**Produced and inspected**  
to ensure current good manufacturing processes (cGMP)<sup>32</sup>



Safety and efficacy **rigorously tested**  
in controlled clinical trials<sup>3,32</sup>



**Consistent dosing**  
and medication concentration in every batch<sup>3</sup>



**Federally legal and available** in all 50 states<sup>3</sup>



**Available**  
with prescription



**Eligible**  
for insurance



Can be **legally transported**  
between states

