Beyond CBD: Chemistry, Exposure, and Toxicity of “Minor” Cannabinoids

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Conflicts of Interest Statement

Presenter has no conflicts of interest to declare
Objectives

Adverse health effects, mechanisms

Molecular structures, origins/sources

Chemistry

Toxicity

Exposure

Consumer products and levels
Chemistry and Origins of Minor Cannabinoids
Scope and Definitions of Minor Cannabinoids

Major cannabinoids: CBD and Δ9-THC

Minor cannabinoids: >100 others

Individual cannabinoids:

- CBG-type
- CBC-type
- CBD-type
- CBN-type
- THC-type

etc...

MM Radwan et al, *Molecules* 2021, 26(9), 2774
KB Walsh et al, *Front Pharmacol* 2021, 12, 777804
Examples of Cannabinoid “Types”

- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Cannabielsoin (CBE)
- Cannabiripsol (CBR)
- Cannabicitran (CBTC)
- Cannabicyclol (CBL)
Examples of CBD-type Cannabinoids
Examples of CBN and THC-type Cannabinoids

CBN

Δ9-THC

Δ8-THC

Δ9-THCV

Δ9-THCA

HHC
Origins of Cannabinoids: Cannabis

Acidic cannabinoids
- CBCA
- CBCVA
- CBDA
- CBDVA
- Δ9-THCA
- Δ9-THCVA

Neutral cannabinoids
- CBC
- CBCV
- CBD
- CBDV
- Δ9-THC
- Δ9-THCV

CBG(V)A
- CBGA
- CBGVA

References:
- MM Radwan et al, Molecules 2021, 26(9), 2774
- KB Walsh et al, Front Pharmacol 2021, 12, 777804
Origins of Cannabinoids: (Semi)synthetic Routes

Acid, solvent, heat → CBD → Δ8 or Δ9-THC → Δ9-THC-O

H₂, C/Pd, EtOH → HHC

Acetic anhydride

δ9-THC analogs
**Origins of Cannabinoids: Synthetic Biology**

Sugar + Fatty acid

Genes from cannabis

Yeast

Cannabinoids

**Complete biosynthesis of cannabinoids and their unnatural analogues in yeast**

**Patent filings for cannabinoid production in yeast**

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2019</td>
<td>3</td>
</tr>
<tr>
<td>2019–2023</td>
<td>62</td>
</tr>
</tbody>
</table>

Google patent search for keyword: “cannabinoid” and classification: "C12N15/81"
Consumer Exposures to Minor Cannabinoids
Minor Cannabinoids in Marketed Products

“In addition to CBD, the current [cannabis derived product] market includes emerging cannabinoids...While the emerging cannabinoid market is still nascent, it is...an emerging public health concern.” (FDA, 2021)
Products Claiming to Contain Minor Cannabinoids

- E-cigarettes
- Foods / Edibles
- Tinctures
- Beverages
- Capsules
- Cosmetics
- Powders
FDA Warns Consumers About the Accidental Ingestion by Children of Food Products Containing THC

June 16, 2022

What's New

This alert has been updated to include new data reported to the FDA and national poison control centers.

Audience

- All consumers

What is the problem?

- Edible products containing tetrahydrocannabinol (THC) can be easily confused with commonly consumed foods such as breakfast cereal, candy, and cookies, especially when packaged to look like toys or small candies.
- Accidental ingestion of these products can lead to serious adverse events in children.
- Some edible products are designed to mimic the appearance of well-known and well-liked foods by using similar brand names, logos, or pictures on their packages. These products can be easily mistaken for popular, well-recognized foods that appeal to children.
- The FDA is aware of reports of copycat products packaged to look like popular brands such as Cocoa Pebbles, Cocoa Puffs, Froot Loops, Fruity Pebbles, Nerds Rope, Sour Patch Kids, and Tris, among others.

Examples of Products

- Cannabutter Gummies
- Crunch Bars

Who is at risk?

The FDA is advising consumers about the risk of accidental ingestion, especially by children, of edible products that contain THC. Accidental ingestion of these edible products may cause serious adverse events.

Summary of Problem and Scope

Some manufacturers are packaging and labeling edible products containing THC to look like popular brands of commonly consumed foods, such as breakfast cereal, candy, and cookies. These products appeal to children and may be easily mistaken for popular, well-recognized foods.

The FDA is aware of multiple media reports describing children and adults who accidentally consumed copycat edible products containing THC and experienced adverse events. Additionally, from January 1, 2021, through May 31, 2022, the FDA received over 125 adverse event reports related to children and adults who consumed edible products containing THC. Some individuals who ate these edible products reportedly experienced adverse events such as hallucinations, increased heart rate and vomiting, and many required medical intervention or hospital admission. Ten of the reports specifically mention the edible product to be a copycat of popular foods, such as Cocoa Pebbles, Gushers, Nerds Rope, Skittles, Sour Patch Kids, and Starburst.
FTC Sends Cease and Desist Letters to Six Companies Selling Edible Products Containing Delta-8 THC, Nearly Identical to Food Children Eat

Commission demands firms immediately change unfair labeling.

The companies’ Delta-8 THC products mimic a range of food that appeal to children. Dr. Smoke, LLC, for example, sells THC-infused “Doritos” that are marketed in packaging that is nearly the same as that of Doritos Nacho Cheese Flavored Tortilla Chips (see graphic), including using the same red background, the use of the Doritos name and triangle logo, and the depiction of two tortilla chips in the same position. In addition, Dr. Smoke’s THC-infused “Cheetos” are sold in packaging that is nearly identical to that of Cheetos Crunchy Flamin’ Hot Cheese Flavored Snacks, right down to the use of the Chester Cheetah mascot.

As part of its ongoing monitoring of health-related advertising claims, the Federal Trade Commission (FTC) today sent cease and desist letters – jointly with the U.S. Food and Drug Administration (FDA) – to six companies currently marketing edible products containing Delta-8 tetrahydrocannabinol (THC) in packaging that is almost identical to many snacks and candy children eat, including Doritos chips, Cheetos cheese-flavored snacks, and Nerds candy.
TECHNICAL REPORT | Hexahydrocannabinol (HHC) and related substances

FIGURE 7b
‘Strawberry Marshmallows HHC’ containing strawberry-shaped HHC-infused sweets. Seized by Swedish Customs in 2022

Source: Swedish Customs.

The size and scale of the retail market is unknown. Products are sold in a range of brick-and-mortar and online shops, particularly those specialised in selling low-THC cannabis and CBD products, as well as vaping products (‘smoke shops’). Initial indications from surface web monitoring suggest that retailers can be found in or ship to most Member States. Producers, retailers, and consumers may also buy bulk oils and finished products from suppliers in the US and import them into Europe. In the latter case, this is supported by information from customs seizures (see Figure 3).
Example of Consumer Product Label Survey

Google search: “buy delta thc”

Top 3 websites (by no. visitors)

804 cannabinoid products
**Examples of Measured Levels in Consumer Products**

*Exposure levels vary in consumer products and labels are often inaccurate*

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Level measured</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBG</td>
<td>51 mg/serving</td>
<td>Edible</td>
</tr>
<tr>
<td>Δ8-THC</td>
<td>17 mg/g</td>
<td>Cookies</td>
</tr>
<tr>
<td>Δ8-THC</td>
<td>13 mg/serving</td>
<td>Several</td>
</tr>
<tr>
<td>HHC</td>
<td>27% w/w</td>
<td>Hemp product</td>
</tr>
<tr>
<td>CBC</td>
<td>1 mg/mL</td>
<td>Oil</td>
</tr>
</tbody>
</table>
Adverse Health Effects and Mechanisms: *In Vivo*
Adverse Health Effects of Δ9-THC

Effects of Δ9-THC, the major cannabinoid in marijuana

Hypothermia, catalepsy, analgesia, ataxia

Intoxication
Memory impairment
Analgesia

Increased heart rate, anxiety, paranoia, psychosis, vomiting, nausea, hypotension, respiratory depression
# Intoxicating Effects of Minor Cannabinoids

Many THC-related cannabinoids cause intoxicating effects in human and/or animal studies.

<table>
<thead>
<tr>
<th>Intoxicating</th>
<th>Not intoxicating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ8-THC</td>
<td>CBC</td>
</tr>
<tr>
<td>Δ9-THC-O</td>
<td>Δ9-THCA</td>
</tr>
<tr>
<td>HHC</td>
<td>CBD</td>
</tr>
<tr>
<td>Δ9-THCB</td>
<td>CBG</td>
</tr>
<tr>
<td>Δ9-THCP</td>
<td></td>
</tr>
</tbody>
</table>
Online Reports of Adverse Health Effects

Adverse effects reported online for minor cannabinoids (e.g., Reddit.com)

“I called 911 and on the way to the ER they told me I might be having a panic attack.” (Δ8-THC)

“The rest of the following day I just felt hungover and sick after it wore off.” (HHCP)

“I get sort of a low grade background anxiety that isn’t usually present when I’m sober.” (Δ9-THC-O)
Poison Control Center Cases

Δ8-THC
National poison control centers (2021)

- 2,362 reports
- 40% pediatric patents
- 70% required evaluation by health care facility
  - 45% pediatric patients
  - 8% critical care

HHC
French poison centres (2022)

- 37 reports
- 50% were moderate or severe
Adverse Health Effects and Mechanisms: *In Vitro*
CB1 Receptor Binding, Double Bonds, and Acid Group

Δ9-THC
Ki ~ 30 nM

Δ8-THC
Ki ~ 30 nM

CBN
Ki ~ 220 nM

HHC
Ki ~ 150 nM

Δ9-THCA-A
Ki ~ 800 nM

EW Bow et al, Persp Med Chem 2016, 8
PB Samson, J Nat Prod 2021, 84, 142-160
RK Razdan, Pharmacol Rev 1986, 38(2), 75-149
**CB1 Receptor Binding and Alkyl Chain Lengths**

*CB1 receptor binding potency increases as alkyl chain length increases*

<table>
<thead>
<tr>
<th>R</th>
<th>Δ9-THC analogue</th>
<th>Ki (nM)</th>
<th>R</th>
<th>Δ8-THC analogue</th>
<th>Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>Δ9-THCV</td>
<td>75</td>
<td>C3</td>
<td>Δ8-THCV</td>
<td>?</td>
</tr>
<tr>
<td>C4</td>
<td>Δ9-THCB</td>
<td>15</td>
<td>C4</td>
<td>Δ8-THCB</td>
<td>65</td>
</tr>
<tr>
<td>C5</td>
<td>Δ9-THC</td>
<td>30</td>
<td>C5</td>
<td>Δ8-THC</td>
<td>44</td>
</tr>
<tr>
<td>C6</td>
<td>Δ9-THCH</td>
<td>?</td>
<td>C6</td>
<td>Δ8-THCH</td>
<td>41</td>
</tr>
<tr>
<td>C7</td>
<td>Δ9-THCP</td>
<td>1</td>
<td>C7</td>
<td>Δ8-THCP</td>
<td>22</td>
</tr>
<tr>
<td>C8</td>
<td>Δ9-THC-jd</td>
<td>?</td>
<td>C8</td>
<td>Δ8-THC-jd</td>
<td>8.5</td>
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## Examples of Other Targets for Minor Cannabinoids

<table>
<thead>
<tr>
<th>Target</th>
<th>Effect</th>
<th>CBG Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic receptor ($\alpha_2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBG: agonist, 10 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin receptor (5-HT1A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBG: antagonist, 50 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptors (PPAR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient receptor potential channels (TRP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoic acid receptors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroidogenic factor-1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arachidonate lipoxygenases*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Predicted by computational methods
Caveats for *In Vitro* Assays: Aggregation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aggregation conc* (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBN</td>
<td>3</td>
</tr>
<tr>
<td>CBGA</td>
<td>29</td>
</tr>
<tr>
<td>CBG</td>
<td>9</td>
</tr>
<tr>
<td>CBDV</td>
<td>11</td>
</tr>
<tr>
<td>CBDA</td>
<td>47</td>
</tr>
<tr>
<td>CBD</td>
<td>12</td>
</tr>
<tr>
<td>CBC</td>
<td>1</td>
</tr>
<tr>
<td>CBCA</td>
<td>32</td>
</tr>
</tbody>
</table>

* Detergent-sensitive malate dehydrogenase inhibition assay
Future Directions and Conclusions
Future Considerations for Minor Cannabinoids

- Confirm potential sources of nonspecific bioactivity (e.g., colloidal aggregation) when studying cannabinoids in vitro
- Profile emerging cannabinoids by new approach methods (in silico, in vitro) or integrated approaches (read across)
- Identify metabolites and their bioactivities compared with parent cannabinoids
- Consider additive (cumulative) pharmacodynamic effects
Conclusions

- Minor cannabinoids are diverse substances associated with cannabis derived consumer products.
- They may be found within the botanical or synthesized and resulting in a wide range of consumer exposure levels.
- Minor cannabinoids can cause intoxicating or non-intoxicating effects.
- Due to their rapid emergence and proliferation, continuing pharmacological and toxicological research is needed to address public health impact of minor cannabinoids.
Acknowledgements