The cannabidiol enigma: are the metabolites of CBD pharmacologically active?

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In terms of publications, research on CBD lags behind THC as reflected by the number of citations in PubMed database. Search terms: ‘THC or tetrahydrocannabinol’ and ‘cannabidiol’.
Cannabidiol monotherapy typically requires large doses

In humans, reported daily oral therapeutic CBD dose range: 15–800 mg

Reasons:

*pharmacodynamics:* low efficacy

*pharmacokinetics:* poor bioavailability

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Reasons: low efficacy and poor bioavailability could be due to metabolism leading to metabolites.
Metabolites of cannabidiol identified in human urine

D. J. HARVEY† and R. MECHOLAM‡

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‡ Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91 120 Israel

33 metabolites identified
4 metabolites partly characterized from the urine of a dystonic patient treated chronically with 600 mg CBD daily
Cannabidiol is extensively oxidized at multiple sites over 35 oxidative human metabolites have been detected\(^1\) + 5 other oxidative derivatives produced \textit{in vitro} by recombinant human CYP450 isoforms\(^2\)

<table>
<thead>
<tr>
<th>CYP450 isoform</th>
<th>Target C-atom</th>
<th>Experimental(^2)</th>
<th>Predicted(^3) (not found by expt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>C6, C7, C1”</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>1A2</td>
<td>C6, C1”–C4”</td>
<td>C6, C7, C8=9, C10, C3”, C4”, C5”</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td>C6, C7, C4”, C5”</td>
<td>C6, C7, C3, C8=9, C10, C4”, C5”</td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>C6, C7, C4”</td>
<td>C6, C7, C8=9, C10, C1”, C3”, C4”, C5”</td>
<td></td>
</tr>
<tr>
<td>2D6</td>
<td>C6, C7, C4”, C5”</td>
<td>C6, C7, C8=9, C10, C1”, C3”, C4”, C5”</td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>C6, C7, C2”, C4”, C5”</td>
<td>C4, C6, C7, C8=9, C3”, C4”, C5”</td>
<td></td>
</tr>
<tr>
<td>3A5</td>
<td>C6, C7, C2”, C3”, C4”</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Harvey & Mechoulam (1990) \textit{Xenobiotica} 20, 303; \(^2\)Jiang \textit{et al} (2011) \textit{Life Sci} 89, 165

\(^3\)CYP450 regioselectivity calculated with StarDrop 6.3 \url{www.optibrium.com/stardrop}
Most abundant oxidative urinary CBD metabolites in a chronic user

alcohols & carboxylic acids include side chain degradants

Bioactivity data are on CBD metabolites are scarce only for 4 single-site oxidative products.

7-COOH-CBD: 1.34%
7-OH-CBD: 0.64%
6α/β-OH-CBD: 0.07%

Relative amount of urinary cannabinoids as determined by Harvey & Mechoulam (1990)
Effects of CBD metabolites on the endocannabinoid system *in vitro*

<table>
<thead>
<tr>
<th>CBD metabolite</th>
<th>Assay <em>in vitro</em></th>
<th>Activity, μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-OH-CBD</td>
<td>CB1/CB2 receptor</td>
<td>Ki &gt; 10</td>
</tr>
<tr>
<td>7-COOH-CBD</td>
<td>CB1/CB2 receptor</td>
<td>Ki &gt; 10</td>
</tr>
<tr>
<td>7-OH-CBD</td>
<td>FAAH inhibition</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; = 34</td>
</tr>
<tr>
<td>7-COOH-CBD</td>
<td>FAAH inhibition</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; &gt; 100</td>
</tr>
<tr>
<td>7-OH-CBD</td>
<td>Anandamide uptake inhibition</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; ~ 50</td>
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</tr>
</tbody>
</table>

## Biological activities of CBD metabolites in animals

<table>
<thead>
<tr>
<th>CBD metabolite</th>
<th>Effect, animal, route of administration</th>
<th>Dose</th>
<th>Degree of activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-OH-CBD</td>
<td>antinociceptive, mouse, ip</td>
<td>20 mg/kg</td>
<td>each fully blocked formalin-induced pain-related behaviour</td>
</tr>
<tr>
<td>7-COOH-CBD</td>
<td>antinociceptive, mouse, ip</td>
<td>20 mg/kg</td>
<td></td>
</tr>
<tr>
<td>7-OH-CBD</td>
<td>antiinflammatory, mouse, ip</td>
<td>40 mg/kg</td>
<td>&lt; 20 mg/kg indomethacin</td>
</tr>
<tr>
<td>7-COOH-CBD</td>
<td>antiinflammatory, mouse, ip</td>
<td>40 mg/kg</td>
<td>≤ 20 mg/kg indomethacin</td>
</tr>
</tbody>
</table>

Anxiolytic & anticonvulsant effects also observed.

Biological activity of CBD metabolites in humans

*Not known*
Similarity of 7-COOH-CBD and the anticonvulsant phenytoin

structural (and pharmacological?)

![Molecular structures of phenytoin and 7-COOH-CBD with highlighted bioisosteric similarity](image)


Molecular modeling by *Discovery Studio Visualizer 4.1* (Accelrys Inc.)
Similarity of 7-COOH-CBD and the anticonvulsant $\Delta^2(E)$-valproate

structural (and pharmacological?)

valproic acid

$\Delta^2(E)$-valproic acid
active metabolite

7-COOH-CBD

common pharmacophore

On valproic acid analogues, see: Bialer et al (1994) Pharm World Sci 16, 2
Molecular modeling by Discovery Studio Visualizer 4.1 (Accelrys Inc.)
SUMMARY

Investigation of CBD metabolites is needed

- identify bioactivity of main metabolites (pharmacological profiling)
- study the involvement of metabolites in CBD’s action in vivo
- explore further therapeutic potential of CBD metabolites
- use single metabolite in therapy (proprietary reasons)