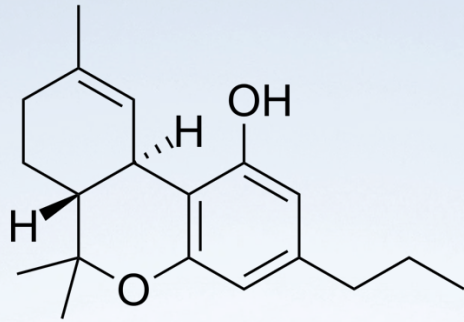


# Tetrahydrocannabivarin ( $\Delta^9$ -THCV)



## White Paper

A curated collection of scientific research studying the physiological and potential therapeutic properties of  $\Delta^9$ -THCV

February 2024



# DISCLAIMER

PLEASE READ CAREFULLY

Tetrahydrocannabinavarin (THCV) has been the subject of a number of clinical trials as well as preclinical research in various disease models. However, it has not been submitted for regulatory approval for any use. This white paper includes a curated list of research on the physiological and potential therapeutic effects of THCV.

Statements contained in this report have not been evaluated by the U.S. Food and Drug Administration (FDA), or other such international regulatory agencies, and are not intended to imply a direct effect on the diagnosis, cure, mitigation, treatment or prevention of any disease.

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Content and supporting selected scientific articles have been reviewed by the scientific teams at BayMedica, LLC (BayMedica) and its parent company, InMed Pharmaceuticals Inc., and have been determined to be sufficiently credible for inclusion.

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## Background

Tetrahydrocannabivarin, also known as THCV, or  $\Delta^9$ -THCV, is a naturally occurring compound of the *Cannabis sativa* plant, and is an analog of the better known major cannabinoid, tetrahydrocannabinol, or THC. While these two cannabinoids share a similar structure and name, they have very different physiological effects. Notably, unlike THC which is an intoxicating Schedule 1 controlled substance in the United States, THCV is non-intoxicating and is legal under the 2018 Farm Bill. In addition, while THC is found abundantly in many strains of the *Cannabis* plant, THCV is a rare, or minor, cannabinoid found in only trace amounts in the plant (Table 1: Differences Between THC and THCV).

THCV was first discovered by scientist Edward Gill in 1970 and named tetrahydrocannabivarin by scientist Frans W. Merkus in 1971.<sup>1</sup> Like other rare cannabinoids, THCV only constitutes a small proportion of the total cannabinoids found in most *Cannabis* plants and as such is difficult and costly to extract directly from the plant. Modern cannabinoid manufacturing technologies, such as biosynthesis and chemical synthesis, both of which are utilized by BayMedica, have enabled production of these rare cannabinoids at commercial quantities, making them cost-effective as core ingredients for various health and wellness applications.

Rare cannabinoids are a class of compounds gaining interest for their potential medical benefits. Of the more than 140 rare cannabinoids found in *Cannabis*, THCV is one of the most well-studied with scientific research showing promising appetite suppressive,<sup>2,3,4,5,6,7,8</sup> anti-inflammatory,<sup>9,10,11,12,13</sup> anti-convulsant,<sup>14,15,16,17</sup> anti-oxidant,<sup>18,19,16</sup> and neuroprotective effects.<sup>18,15,16,20</sup> THCV has been researched extensively for its appetite suppression effects that are attributed to THCV's interaction with specific receptors involved with rewarding stimuli, making it an interesting compound for use in weight management. In addition to obesity, THCV has also been the subject of studies in diabetes,<sup>2,7</sup> epilepsy,<sup>14,15,16,17</sup> acne,<sup>2</sup> pain,<sup>15,16</sup> Parkinson's disease,<sup>18,19</sup> osteoarthritis<sup>16,21</sup> and nausea.<sup>22</sup>

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<sup>1</sup> Br J Pharmacol. 2005 Dec; 146(7): 917–926. Published online 2005 Oct 3. doi: 10.1038/sj.bjp.0706414

<sup>2</sup> Journal of Cannabis Research volume 2, Article number: 6 (2020)

<sup>3</sup> PeerJ. 2020 Aug 24;8:e9811. doi: 10.7717/peerj.9811. eCollection 2020

<sup>4</sup> Br J Pharmacol. 2009 Apr;156(7):1154-66. doi: 10.1111/j.1476-5381.2008.00107.x.

<sup>5</sup> J Hepatol. 2015 Jun;62(6):1382-90. doi: 10.1016/j.jhep.2015.01.001. Epub 2015 Jan 13

<sup>6</sup> Int J Neuropsychopharmacol. 2014 Dec 25;18(6):pyu094. doi: 10.1093/ijnp/pyu094.

<sup>7</sup> Diabetes Care. 2016 Oct;39(10):1777-86. doi: 10.2337/dc16-0650.2016 Aug 29

<sup>8</sup> Nutr Diabetes. 2013 May 27;3(5):e68. doi: 10.1038/nutd.2013.9.

<sup>9</sup> Exp Dermatol. 2016 Sep;25(9):701-7. doi: 10.1111/exd.13042. Epub 2016 Jun 15

<sup>10</sup> Br J Pharmacol. 2008 Jan;153(2):199-215. doi: 10.1038/sj.bjp.0707442. Epub 2007 Sep 10

<sup>11</sup> Pharmacol Res. 2016 Nov;113(Pt A):199-208. doi: 10.1016/j.phrs.2016.07.045. Epub 2016 Aug 3

<sup>12</sup> Br J Pharmacol. 2019 May;176(10):1568-1584. doi: 10.1111/bph.14460. Epub 2018 Sep 9.

<sup>13</sup> Front Pharmacol. 2021; 12: 777804. 2021 Nov 29. doi: 10.3389/fphar.2021.777804

<sup>14</sup> Epilepsia. 2010 Aug;51(8):1522-32. doi: 10.1111/j.1528-1167.2010.02523.x. Epub 2010 Feb 26

<sup>15</sup> Sci Rep. 2020 Nov 23;10(1):20405. doi: 10.1038/s41598-020-77175-y

<sup>16</sup> J Nat Prod. 2021 Jan 22;84(1):142-160. doi: 10.1021/acs.jnatprod.0c00965. Epub 2020 Dec 23

<sup>17</sup> Int J Environ Res Public Health. 2021 Apr; 18(8): 3993.

<sup>18</sup> Neurobiol Dis. 2020 Jul;141:104892. doi: 10.1016/j.nbd.2020.104892. Epub 2020 May 6.

<sup>19</sup> Br J Pharmacol. 2011 Aug;163(7):1495-506. doi: 10.1111/j.1476-5381.2011.01278.

<sup>20</sup> Br J Pharmacol. 2020 Oct; 177(19): 4330–4352. Published online 2020 Sep 1. doi: 10.1111/bph.15185

<sup>21</sup> Pharmacol Res. 2018 Oct;136:83-89. doi: 10.1016/j.phrs.2018.08.021. Epub 2018 Aug 28.

<sup>22</sup> Comparative Study Br J Pharmacol. 2013 Oct;170(3):671-8. doi: 10.1111/bph.12322.

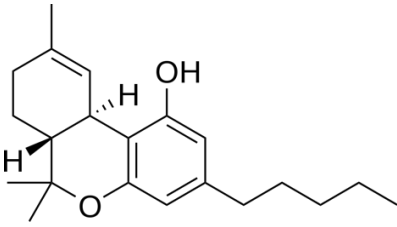
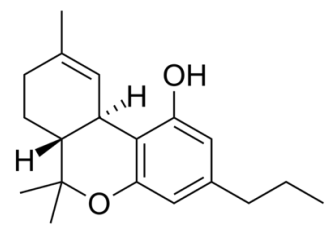
| THC   | THCV  |
|---|---|
|  <ul style="list-style-type: none"> <li>• Five carbon sidechain</li> </ul> |  <ul style="list-style-type: none"> <li>• Three carbon sidechain</li> </ul> |
| <ul style="list-style-type: none"> <li>• Major cannabinoid, found abundantly in the <i>Cannabis sativa</i> plant</li> </ul>                                 | <ul style="list-style-type: none"> <li>• Rare, or minor, cannabinoid, found in trace amounts in the <i>Cannabis sativa</i> plant</li> </ul>                   |
| <ul style="list-style-type: none"> <li>• Intoxicating, euphoric effects</li> </ul>  | <ul style="list-style-type: none"> <li>• Non-intoxicating</li> </ul>  |
| <ul style="list-style-type: none"> <li>• A Schedule 1 controlled substance and therefore federally illegal</li> </ul>                                       | <ul style="list-style-type: none"> <li>• Not a scheduled substance and is legal under the 2018 Farm Bill</li> </ul>   |

TABLE 1: DIFFERENCES BETWEEN THC AND THCV

### What is the difference between Delta8-THCV and Delta9-THCV?

Delta-9-THCV ( $\Delta 9$ -THCV) and Delta-8-THCV ( $\Delta 8$ -THCV) have the same molecular composition, but their compound structure is different by the position of one double-bond (Figure 1).  $\Delta 9$ -THCV is naturally produced by the *Cannabis sativa* plant in very small quantities. Conversely,  $\Delta 8$ -THCV is not produced by the plant, but instead is the result of degradation of  $\Delta 9$ -THCV to  $\Delta 8$ -THCV (technically, isomerization causes the double bond to move to a more thermodynamically stable position).

One of the distinct differences between  $\Delta 9$ -THCV and  $\Delta 8$ -THCV is that  $\Delta 9$ -THCV is more difficult to manufacture compared to  $\Delta 8$ -THCV due to the fact that  $\Delta 8$ -THCV is thermodynamically favored.<sup>23</sup> Most of the scientific research into the effects and potential therapeutic properties of THCV has used  $\Delta 9$ -THCV, either synthesized or plant-derived. BayMedica manufactures  $\Delta 9$ -THCV.

It is hypothesized that since  $\Delta 9$ -THC is more potent than  $\Delta 8$ -THC, the same may be true for  $\Delta 9$ -THCV versus  $\Delta 8$ -THCV. However, there is minimal research comparing the two compounds.

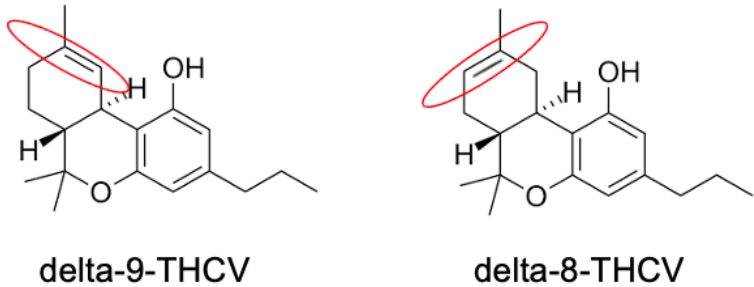


FIGURE 1: DELTA-9-THCV AND DELTA-8-THCV MOLECULAR STRUCTURE

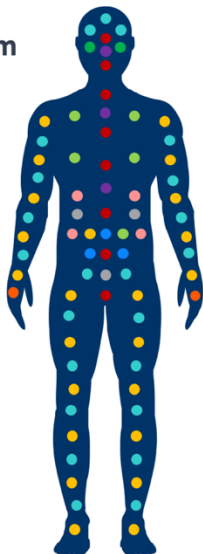
<sup>23</sup> Comparative Study Br J Pharmacol. 2007 Mar;150(5):586-94. doi: 10.1038/sj.bjp.0707124. Epub 2007 Jan 22.

## The Endocannabinoid System

Since the discovery of the endocannabinoid system in the 1990s, mounting research into the physiological effects of cannabinoids has made them an important therapeutic target for several conditions. The endocannabinoid system impacts a broad range of physiological processes. Cannabinoids act as messengers that bind to cannabinoid receptors, as well as other receptors, signaling the endocannabinoid system into action. Cannabinoid receptors are found throughout the body and are involved in brain function, immune function, pain perception and inflammation (Figure 2).

### The Endocannabinoid System

- **CB1**  
Receptors concentrated in the brain and central nervous system but are also present in some nerves and organs
- **CB2**  
Receptors mostly found in peripheral organs, especially cells associated with the immune system
- **TRPA1**  
Receptors found primarily in peripheral sensory cells
- **GPR6**  
Receptors mainly expressed in the brain, particularly in the striatum.
- **GPR55**  
Receptors found in the bones, the brain (particularly the cerebellum), and the jejunum and ileum



- **TRPV1**  
Receptors concentrated in the blood, bone, marrow, tongue, kidney, liver, stomach & ovaries
- **TRPV2**  
Receptors concentrated in the skin, muscle, kidney, stomach & lungs
- **TRPV5**  
Receptors concentrated predominantly in the kidney as well as the intestine
- **TRPV6**  
Receptors found primarily in the intestine, but also expressed in the kidney
- **2-AG**  
Endocannabinoid associated with the central nervous system and brain

FIGURE 2: THE ENDOCANNABINOID SYSTEM (NOT EXHAUSTIVE)

## THCV Interaction with the Human Endocannabinoid System

Scientific literature suggests that THCV acts as an antagonist of cannabinoid receptor 1 (CB1), TRPV5 and TRPV6, as an agonist of cannabinoid receptor 2 (CB2), TRPV1, GPR55 and TRPA1, and inhibits 2-AG production (Figure 3). These receptors and endocannabinoids are involved in a variety of physiological functions in the body (Table 2: Human Receptors and Endocannabinoids Interacting with THCV).

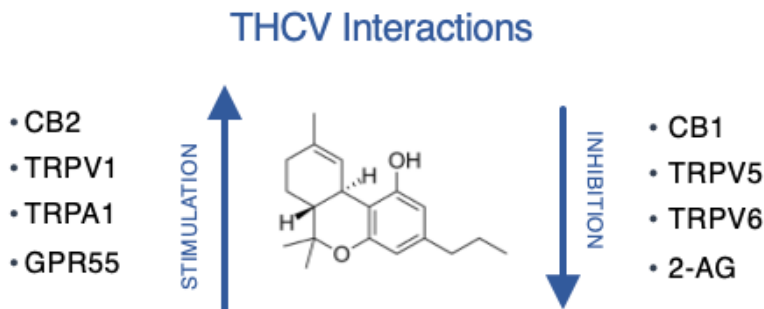


FIGURE 3: EFFECTS OF Δ9-THCV ON HUMAN RECEPTORS AND ENDOCANNABINOID

## Description of Receptors and Endocannabinoids Involved with THCV

| Receptor / Endocannabinoid                              | Location in the body  | Physiological function  |
|---|---|---|
| <b>Transient receptor potential ankyrin 1 (TRPA1)</b>   | TRPA1 receptors are found in the peripheral sensory cells.  | <ul style="list-style-type: none"> <li>• Pain</li> <li>• Inflammation</li> <li>• Cold sensation</li> <li>• Hearing</li> </ul>         |
| <b>Transient receptor potential vanilloid 1 (TRPV1)</b> | TRPV1 receptors, also known as a capsaicin receptor, are concentrated in the blood, bone, marrow, tongue, kidney, liver, stomach and ovaries.   | <ul style="list-style-type: none"> <li>• Pain</li> <li>• Heat sensation</li> <li>• Immune function</li> <li>• Inflammation</li> </ul> |
| <b>Transient receptor potential vanilloid 5 (TRPV5)</b> | TRPV5 receptors are mainly concentrated in the kidney, but also expressed in the intestine.   | <ul style="list-style-type: none"> <li>• Kidney function</li> <li>• Bone density</li> </ul>   |
| <b>Transient receptor potential vanilloid 6 (TRPV6)</b> | TRPV6 receptors are mainly concentrated in the intestine, but also expressed in the kidney.   | <ul style="list-style-type: none"> <li>• Kidney function</li> <li>• Bone density</li> </ul>   |
| <b>G protein-coupled receptor 55 (GPR55)</b>            | GPR55 receptors are mainly expressed in the brain and central nervous system, and are also found in the gastrointestinal tract, lung, liver, bladder, kidney, uterus, adrenal glands. | <ul style="list-style-type: none"> <li>• Gastrointestinal</li> <li>• Pain</li> <li>• Inflammation</li> </ul>                          |
| <b>Cannabinoid receptor type 1 (CB1)</b>                | CB1 receptors are concentrated in the brain and central nervous system but are also present in the skeletal muscle, liver and pancreas.   | <ul style="list-style-type: none"> <li>• Neurophysiological</li> <li>• Neurodegenerative</li> </ul>                                   |
| <b>Cannabinoid receptor type 2 (CB2)</b>                | CB2 receptors are mainly expressed in immune cells and also expressed in the cardiovascular system, gastrointestinal tract, liver, bone and reproductive system.                      | <ul style="list-style-type: none"> <li>• Immune function</li> <li>• Pain</li> <li>• Inflammation</li> </ul>                           |
| <b>2-Arachidonoylglycerol (2-AG)</b>                    | 2-AG endocannabinoid is associated with the central nervous system and brain.   | <ul style="list-style-type: none"> <li>• Neuronal</li> <li>• Pain</li> <li>• Inflammation</li> <li>• Energy</li> </ul>                |

TABLE 2: HUMAN RECEPTORS AND ENDOCANNABINOIDS INTERACTING WITH THCV

## Tetrahydrocannabivarin Molecular Structure and Compound Information

$\Delta^9$ -THCV is a propyl analog of THC and has a similar molecular structure to THC but with a shorter three carbon sidechain compared to THC's five carbon sidechain (Table 3:  $\Delta^9$ -THCV Molecular Structure and Compound Information (Source: Pubchem)).

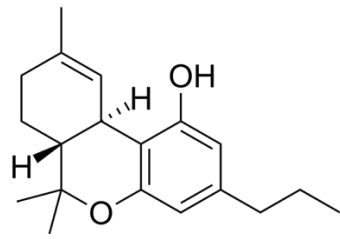
|                           |  |
|---------------------------|--|
| Molecular structure       |   |
| Molecular formula         | C <sub>19</sub> H <sub>26</sub> O <sub>2</sub>   |
| Molecular weight          | 286.4 g/mol  |
| IUPAC Name                | (6aR,10aR)-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol  |
| DrugBank Accession Number | DB11755  |
| CAS                       | 31262-37-0   |
| Pubchem CID               | 93147  |
| Other names               | TETRAHYDROCANNABIVARIN<br>THCV<br>THC-V<br>delta9-Tetrahydrocannabivarin<br>$\Delta^9$ -Tetrahydrocannabivarin<br>delta9-THCV<br>$\Delta^9$ -THCV<br>31262-37-0<br>UNII-I5YE3I47D8<br>(6aR,10aR)-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol<br>I5YE3I47D8<br>GWP42004<br>GWP-42004 |

TABLE 3:  $\Delta^9$ -THCV MOLECULAR STRUCTURE AND COMPOUND INFORMATION (SOURCE: [PUBCHEM](#))



## Research into the Effects of $\Delta$ 9-Tetrahydrocannabivarin

$\Delta$ 9-THCV is one of the most well-studied rare cannabinoids. Interest in  $\Delta$ 9-THCV has grown significantly over the last several years as scientific evidence has shown its appetite suppression effects.<sup>2,3,4,5,6,7,8</sup> Evidence indicates that  $\Delta$ 9-THCV also exhibits anti-inflammatory,<sup>9,10,11,12,13</sup> anti-convulsant,<sup>14,15,16,17</sup> anti-oxidant<sup>18,19,16</sup> and neuroprotective effects.<sup>18,15,16,20</sup>  $\Delta$ 9-THCV has been researched for its ability to reduce weight and increase energy. This effect can be attributed to  $\Delta$ 9-THCV's interaction with specific receptors involved with rewarding stimuli.  $\Delta$ 9-THCV has been the subject of studies in obesity,<sup>2,3,4,5,6,7,8</sup> diabetes,<sup>2,7</sup> epilepsy,<sup>14,15,16,17</sup> acne,<sup>2</sup> pain,<sup>15,16</sup> Parkinson's disease,<sup>18,19</sup> osteoarthritis,<sup>16,21</sup> and nausea.<sup>22</sup>

### $\Delta$ 9-THCV Therapeutic Research – A Summary of Scientific Publications

$\Delta$ 9-THCV has been studied for its potential therapeutic benefits in several conditions as summarized below.

#### Appetite Suppression

According to the U.S. Centers for Disease Control and Prevention, the prevalence of obesity in the U.S. was 42.4% (137.8 million Americans) in 2017-2018. Obesity is one of the leading causes of preventable, premature death and it can lead to several other conditions including heart disease, stroke and type 2 diabetes. The toll on the health system is staggering with an estimated annual cost of \$147 billion in 2008 in the U.S. alone. The CDC estimates medical costs for people who had obesity was \$1,429 higher than for those with a healthy weight.

Over the last decade, there has been significant interest in  $\Delta$ 9-THCV for its appetite suppression effects. Much of the research surrounding  $\Delta$ 9-THCV has been to study its hypophagic (appetite suppressing) properties and its interaction with cannabinoid receptors involved in food-seeking behaviors and reward. Researchers believe that CB1 neutral antagonists, such as  $\Delta$ 9-THCV, may be a safer alternative to CB1 inverse agonists, such as rimonabant, an anorectic anti-obesity treatment produced by Sanofi-Aventis that was withdrawn in 2008 due to psychiatric side effects. Studies show that while  $\Delta$ 9-THCV reduces weight gain and food intake as rimonabant does,  $\Delta$ 9-THCV does not affect emotional regulation as seen with CB1 inverse agonists such as rimonabant. Mounting evidence of  $\Delta$ 9-THCV's ability to increase energy levels and reduce weight, along with its safety profile, has made this rare cannabinoid an interesting target for weight loss.

In a double-blinded, placebo-controlled human study of 20 participants,  $\Delta$ 9-THCV increased neural responding to food reward and aversive stimuli, suggesting therapeutic effect in obesity. The findings, documented in the scientific article entitled "*Neural Effects of Cannabinoid CB1 Neutral Antagonist Tetrahydrocannabivarin on Food Reward*,"<sup>6</sup> demonstrated that  $\Delta$ 9-THCV activated regions of the brain associated with reward processing. The researchers suggest that obese individuals typically have a reduced response to reward and that  $\Delta$ 9-THCV may produce a more pronounced enhancement of reward response, thus could act to rebalance the food reward system and reduce overeating that may occur due to overcompensation. The researchers believe that as a neutral CB1 antagonist,  $\Delta$ 9-THCV may be a safer alternative to rimonabant which is a CB1 inverse agonist. While  $\Delta$ 9-THCV can produce the same appetite suppression and weight loss effects as rimonabant, it is not expected to induce the depressive effects seen with rimonabant. As a CB1 inverse agonist, it is suggested that rimonabant suppresses emotion regulation, potentially leading to the depressive effects. As a neutral CB1 receptor

antagonist, it is suggested that  $\Delta 9$ -THCV would keep neural reward responses but augment aversive responses. The double-blind study involved 20 participants who were randomized to 10mg of  $\Delta 9$ -THCV or placebo. Researchers found those who had  $\Delta 9$ -THCV had increased neural responding to rewarding and aversive stimuli, suggesting therapeutic activity in obesity with a potential lowered risk of depressive effects.

Another study involving 20 healthy individuals demonstrated  $\Delta 9$ -THCV's ability to regulate the activity in regions of the brain which are typically increased in obese individuals. The results were described in a scientific article entitled "*The CB1 Neutral Antagonist Tetrahydrocannabivarin Reduces Default Mode Network and Increases Executive Control Network Resting State Functional Connectivity in Healthy Volunteers.*"<sup>24</sup> Participants were randomized to 10mg of  $\Delta 9$ -THCV or placebo.  $\Delta 9$ -THCV demonstrated an ability to reduce resting state functional connectivity in the left amygdala and parts of default mode network (DMN) of the brain, which are involved in visual responses to food cues and tastes. Researchers note that obese individuals typically have increased activity in these regions of the brain. The results suggest that  $\Delta 9$ -THCV may be able to regulate functional connectivity in parts of the brain which are typically altered in obese individuals.

Reduced weight and increased energy were demonstrated in an *in vivo* study of  $\Delta 9$ -THCV entitled "*The cannabinoid  $\Delta 9$ -tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity.*"<sup>8</sup> In the study,  $\Delta 9$ -THCV was shown to reduce body fat content and increase energy expenditure by up to 17.1%. In addition,  $\Delta 9$ -THCV reduced fasting insulin levels and liver triglyceride levels, demonstrating promising findings that serve as rationale for the development of  $\Delta 9$ -THCV as a potential treatment for obesity.

Research results from the study "*Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis*"<sup>5</sup> showed that  $\Delta 9$ -THCV was able to increase glucose tolerance and lower lipid levels, a therapeutic profile that is favorable for anti-obesity.

Researchers observed suppressed food intake and weight reduction in a study of pure  $\Delta 9$ -THCV. The study "*Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice*"<sup>4</sup> showed that  $\Delta 9$ -THCV induces appetite suppression properties and significantly reduces body weight.

Two scientific articles "*Phytocannabinoid Pharmacology: Medicinal Properties of Cannabis sativa Constituents Aside from the "Big Two"*,"<sup>16</sup> and " *$\Delta 9$ -Tetrahydrocannabivarin (THCV): a commentary on potential therapeutic benefit for the management of obesity and diabetes,*"<sup>2</sup> reviewed the accumulated research on  $\Delta 9$ -THCV's impact on food response and weight reduction and its safety profile. They conclude that as a neutral CB1 antagonist,  $\Delta 9$ -THCV shows promise as an anti-obesity treatment with a favorable safety profile.

## Diabetes

An estimated 37.3 million Americans have diabetes, about 11% of the U.S. population, according to the American Diabetes Association. Diabetes was the 7<sup>th</sup> leading cause of death in the U.S. in 2019. It is estimated that the total costs associated with diabetes was \$327 billion in the U.S. in 2017.

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<sup>24</sup> Int J Neuropsychopharmacol. 2015 Sep 10;19(2):pyv092. doi: 10.1093/ijnp/pyv092.

In parallel with studies on  $\Delta 9$ -THCV's appetite suppression and weight loss effects, this rare cannabinoid has also been studied as a potential treatment for diabetes. Obesity and type 2 diabetes are conditions that are highly prevalent together and share similar characteristics as to the causes that lead to these conditions, such as food control. Beneficial effects of either condition tend to improve the outcome of the other. As such, many of the studies supporting  $\Delta 9$ -THCV's beneficial effects on obesity have demonstrated a positive outcome for diabetes. Human clinical studies, as well as supporting *in vivo* studies have demonstrated  $\Delta 9$ -THCV's effects on improving glycemic control, significantly reducing blood glucose concentrations and improving insulin sensitivity – all important factors in controlling diabetes.

Type 2 diabetes is the only condition in which  $\Delta 9$ -THCV has been studied in a Phase 2 human clinical trial. The 15-19 week Phase 2 clinical trial conducted by GW Pharma Ltd (now Jazz Pharmaceuticals) involving 62 patients with type 2 diabetes, studied participants' cholesterol levels, body weight, liver fat content and other metabolic parameters comparing  $\Delta 9$ -THCV, CBD and placebo. Results showed that compared with placebo,  $\Delta 9$ -THCV significantly decreased fasting plasma glucose, improved pancreatic  $\beta$ -cell function and significantly increased adiponectin concentrations, which is typically reduced in type 2 diabetes and obesity. Results from the study were published in a scientific article "*Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study.*"<sup>27</sup> In the study, there were five treatment arms, including one group randomized to 5mg of  $\Delta 9$ -THCV, twice daily.  $\Delta 9$ -THCV was able to improve glycemic control, while CBD failed to show any metabolic effects. Researchers conclude that  $\Delta 9$ -THCV could represent a new treatment option in glycemic control for patients with type 2 diabetes.

In the study "*Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes,*"<sup>25</sup> researchers point to  $\Delta 9$ -THCV's interaction with cannabinoid receptor TRPV1 for its potential to restore insulin sensitivity and modulate metabolic processes important in the control of diabetes.

According to the study "*Phytocannabinoids promote viability and functional adipogenesis of bone marrow-derived mesenchymal stem cells through different molecular targets,*"<sup>26</sup> individuals with specific metabolic disorders, like type 2 diabetes, have altered functions in bone marrow-derived mesenchymal stem cells (BM-MSCs). In their study,  $\Delta 9$ -THCV was shown to increase the number of viable BM-MSCs, suggesting its potential to re-establish energy metabolism homeostasis.

In another study looking into lipid levels and the regulation of body energy homeostasis, "*Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis,*"<sup>25</sup>  $\Delta 9$ -THCV was shown to reduce accumulated lipid levels and inhibited the development of hepatosteatosis, which is the build-up of fat in the liver, often associated with type 2 diabetes and obesity. These results show further evidence of  $\Delta 9$ -THCV's potential as a treatment option to control diabetes.

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<sup>25</sup> Br J Pharmacol. 2011 Aug;163(7):1479-94. doi: 10.1111/j.1476-5381.2010.01166.x.

<sup>26</sup> Biochem Pharmacol. 2020 May;175:113859. doi: 10.1016/j.bcp.2020.113859. Epub 2020 Feb 14.

## Epilepsy

An estimated 65 million people worldwide and 3.4 million Americans have epilepsy according to the Epilepsy Foundation. Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures. It is the fourth most common neurological condition.

Epilepsy is one of the few conditions for which there is an approved cannabinoid-based treatment. Epidiolex® (manufactured by GW Pharmaceuticals, now part of Jazz Pharmaceuticals) is a pharmaceutical preparation of highly purified, plant-derived cannabidiol (CBD) liquid formulation approved by the U.S. Food and Drug Administration in June 2018 for the treatment of two rare and severe forms epilepsy, Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older. In 2020, it was also approved by FDA for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older.

The relevance of the endocannabinoid system on neurological activity has made cannabinoids an interesting therapeutic target for epilepsy.  $\Delta 9$ -THCV is one of the few rare cannabinoids that has been studied for its anti-seizure effects. A number of *in vivo* and *in vitro* studies have demonstrated  $\Delta 9$ -THCV's anti-epileptiform and anti-convulsant properties.

Promising research results from the study "*D9-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats*"<sup>14</sup> demonstrated that  $\Delta 9$ -THCV significantly reduced seizure incidence and burst complex and exerts anti-epileptiform and anti-convulsant properties, supporting  $\Delta 9$ -THCV's potential as a treatment for epilepsy.

The study "*The phytocannabinoid D9-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum*"<sup>27</sup> further supports  $\Delta 9$ -THCV's anti-convulsant effects. According to study,  $\Delta 9$ -THCV improves inhibitory neurotransmission, ultimately facilitating the control of posture and movement. The results suggest that  $\Delta 9$ -THCV may have therapeutic potential in diseases involving cerebellar dysfunction and hyperexcitability, such as epilepsy.

## Anti-Inflammation and Skin conditions (Acne)

The endocannabinoid system influences a wide variety of physiological functions, including maintenance of the skin. Research has demonstrated that  $\Delta 9$ -THCV may have anti-inflammatory properties.<sup>9,10,11,28</sup>  $\Delta 9$ -THCV has been explored for its potential as an anti-acne agent as well as other skin conditions. In a study of a several non-intoxicating cannabinoids, "*Differential effectiveness of selected non-psychotropic phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrheic skin and acne treatment*,"<sup>9</sup>  $\Delta 9$ -THCV exerted remarkable anti-inflammatory actions and significantly reduce 'acne-like' lipogenesis. Researchers suggest that  $\Delta 9$ -THCV, in particular, shows promise as an anti-acne agent.<sup>9</sup>

## Pain

$\Delta 9$ -THCV has been studied for its potential to reduce pain symptoms. In a recent study, "*In vitro and in vivo pharmacological activity of minor cannabinoids isolated from Cannabis sativa*"<sup>15</sup>  $\Delta 9$ -THCV produced a dose-dependent increase in anti-nociceptive effects, suggesting the possibility of  $\Delta 9$ -THCV's use in managing pain. Another study "*Phytocannabinoid Pharmacology: Medicinal Properties of Cannabis*

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<sup>27</sup> Br J Pharmacol. 2008 May; 154(1): 204–215. Published online 2008 Mar 3. doi: 10.1038/bjp.2008.57

<sup>28</sup> Molecules. 2021 Sep 2;26(17):5352. doi: 10.3390/molecules26175352.

sativa Constituents Aside from the “Big Two”,<sup>16</sup> suggests that Δ9-THCV’s interaction with GPR55 receptor contributes to its pain-relieving properties.

### Osteoarthritis

A recently published scientific article “Phytocannabinoid Pharmacology: Medicinal Properties of Cannabis sativa Constituents Aside from the “Big Two”,<sup>16</sup> points to the inhibition of cannabinoid receptor TRPV5 as a potential therapeutic target for osteoarthritis. Scientific research indicates that Δ9-THCV inhibits TRPV5.<sup>21</sup>

## Current Clinical Studies of THCV

THCV has been studied in clinical trials for diabetes and dyslipidemia and there is an active clinical trial of THCV for androgenetic alopecia as well as a Phase 1 safety study (Table 4). Currently, there is no regulatory approved use of THCV for any condition.

The following clinical trials using THCV are being conducted as of the time this white paper was published. Study information is taken directly from [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

| Condition  | Study information  |
|--|--|
| <b>Safety study</b><br>Sponsor: Canopy Growth Corporation                                  | <b>Phase 1</b><br>This is a two-phase, randomized, double-blind, placebo-controlled, within-participant crossover study to assess the safety, tolerability, PK, and PD of five oral doses of CHI-915 versus placebo in healthy adult participants ages 18-55 years.  |
| <b>Androgenetic Alopecia</b><br>Sponsor: Hair and Scalp Clinic / Gregory L. Smith, MD, MPH | <b>Early Phase 1</b><br>The study is a case series of adults (males and females) presenting to a "Hair and Scalp" center in Clearwater, Florida. Subjects diagnosed with androgenetic alopecia (AGA - male pattern baldness) and who were not currently using minoxidil or finasteride, were offered the opportunity to receive a topical hemp-oil extract that is high in varins (tetrahydrocannabivarin (THCV), cannabidivarin (CBDV)) as well as cannabidiol (CBD).   |
| <b>Weight Loss</b><br>Sponsor: Medical Life Care Planners, LLC                             | <b>Early Phase 1</b><br>The study is to compare two doses of THCV on healthy non-diabetic obese adults and determine if THCV is superior to placebo for losing weight, abdominal girth, cholesterol levels and blood glucose.  |
| <b>Motivation, Energy Level, Focus and Appetite</b><br>Sponsor: Phylos Bioscience, Inc.    | <b>Observational</b><br>The rationale for this study is to determine the effect of a consumer-grade, state-legal formulation of cannabinoids including Tetrahydrocannabivarin (THCV) on motivation, energy level, focus, and appetite. The investigators will examine the outcomes in a broad age-range of adults who have chosen to try these products. The study will incorporate participant reported outcomes and surveys collected after each product use session to engage the participant in their typical day-to-day activities. |

TABLE 4: CURRENT CLINICAL STUDIES OF THCV

## $\Delta$ 9-THCV Human Safety Studies

### $\Delta$ 9-THCV is Well-tolerated in Human Studies

Human safety studies of THCV have been conducted in a Phase 1 and Phase 2 clinical trials by GW Research. In the Phase 2 clinical study of 62 patients,  $\Delta$ 9-THCV was well-tolerated in dosages of up to 5mg twice daily. No safety concerns were identified in the study. Another placebo-controlled, double-blind study involving 10 participants showed that 10mg of  $\Delta$ 9-THCV was well-tolerated and subjectively indistinguishable from placebo.

The current clinical safety study by Canopy Growth and the alopecia study by the Hair and Scalp Clinic will provide additional safety data related to  $\Delta$ 9-THCV. Canopy Growth's safety study will evaluate 12.5mg to 200 mg single oral administration of THCV in oil.

The alopecia clinical trial by the Hair and Scalp Clinic will evaluate a skin topical mix of CBDV and THCV at 500mg and 1000 mg applied to the scalp.

## Specifications

BayMedica manufactures a highly pure  $\Delta 9$ -THCV. Our cannabinoids are manufactured to a high quality and are made following food-grade GMP (Good Manufacturing Practice) standards for the health and wellness sector. Our reproducible process guarantees the purity, quality and consistency of our THCV and reduces any batch-to-batch variability. Furthermore, our production methods can be scaled up to meet demand to ensure our clients have an ongoing supply of  $\Delta 9$ -THCV without supply chain concerns.

Each batch of our highly pure  $\Delta 9$ -THCV is analyzed by certified independent analytical laboratories to assess its potency and to test for residual solvents, heavy metals, pesticides, microbial activity and mycotoxins. In addition, BayMedica's  $\Delta 9$ -THCV is THC-free.

Certificates of Analysis are available upon request.

## Sales Inquiries

BayMedica is a leading large-scale supplier of rare cannabinoids and has bulk highly pure  $\Delta 9$ -THCV available wholesale as a raw ingredient. Interested in purchasing wholesale THCV for your health and wellness products? You can initiate an order by emailing [orders@baymedica.com](mailto:orders@baymedica.com).