

# The Dual-Pathway Mechanism of Cannabidiol: Metabolic Resilience as a Context-Dependent Determinant of Cytotoxicity

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February 13, 2026

## Abstract

The European Food Safety Authority (EFSA) recently set a provisional safety limit for cannabidiol (CBD) at 2 mg/kg/day, citing hepatotoxicity concerns and data gaps. This uniform approach overlooks CBD's biphasic pharmacodynamics. We hypothesize that CBD induces universal mitochondrial stress via voltage-dependent anion channels (VDAC1/VDAC2), with cellular outcome (survival versus apoptosis) determined by glutathione (GSH) buffering capacity rather than target selectivity. Using a deterministic kinetic model (*In Silico* Model V4: Honest-Resilience), we simulated supratherapeutic CBD ( $> 10 \mu\text{M}$ ) effects on mitochondrial membrane potential ( $\Delta\Psi_m$ ) and reactive oxygen species (ROS) in contrasting metabolic phenotypes. VDAC engagement was universal, yet healthy hepatocytes neutralized the ROS spike ( $\Delta\Psi_m$  stabilized at +1.54 arbitrary units,  $\text{ROS} \leq 0.24$ ), while compromised phenotypes collapsed ( $\Delta\Psi_m - 47.6$ ,  $\text{ROS} > 1.5$ ). CBD toxicity therefore reflects conditional bioenergetic failure. We propose risk-stratified dosing guided by metabolic health rather than absolute dose.

**Keywords:** cannabidiol, VDAC1, glutathione, mitochondrial stress, in silico toxicology, risk-stratified dosing

## 1. Introduction

Recent EFSA regulatory decisions highlight a “safety paradox” for CBD: high doses (10–20 mg/kg) are required for clinical efficacy in severe epilepsy, yet toxicological studies suggest risk of liver injury [1]. This discrepancy arises from oversimplified views of CBD's molecular interactions. Described as a promiscuous lipophile ( $\text{LogP} \approx 6.3$ ), CBD partitions readily into mitochondrial membranes.

We resolve this by distinguishing two concentration-dependent pathways:

1. **Therapeutic pathway** ( $< 5 \mu\text{M}$ ): high-affinity receptor interactions (TRPV1, 5-HT1A) promote homeostasis.

2. **Cytotoxic pathway** ( $> 10 \mu\text{M}$ ): direct VDAC1 engagement causes membrane uncoupling [2].

Rather than viewing toxicity as intrinsic, we test whether it represents a conditional failure of bioenergetic resilience.

## 2. Methods: In Silico Systems Biology

### 2.1. Model Architecture

A system of ordinary differential equations (ODEs) tracks:

- Mitochondrial membrane potential ( $\Delta\Psi_m$ ), maintained by respiration and drained by VDAC conductance.

- ROS generation proportional to VDAC leak, removed by a scavenging term ( $S_{cap}$ ).
- Apoptotic trigger when  $\Delta\Psi_m < 0.4$  or  $ROS > 2.0$  (arbitrary units).

## 2.2. Parameterization

Parameters were derived from literature consensus using the IRIS-Gate-Evo protocol:

- $K_d$  (CBD–VDAC1)  $\approx 11.0 \mu\text{M}$ .
- **Healthy phenotype:** high metabolic reserve,  $S_{cap} = 3.0$ .
- **Vulnerable phenotype:** low reserve,  $S_{cap} = 0.6$ .

## 3. Results

### 3.1. Selective Toxicity Threshold

A high-dose challenge ( $40 \mu\text{M}$  CBD) produced divergent outcomes:

- **Vulnerable phenotype** (e.g., cancer/NAFLD): VDAC saturation caused rapid ROS release, overwhelming depleted scavenging capacity and collapsing  $\Delta\Psi_m$  ( $-47.6$ ) with immediate apoptosis.
- **Healthy phenotype:** identical VDAC occupancy yielded stable  $\Delta\Psi_m$  ( $+1.54$ ) as robust GSH reserves buffered ROS (peak  $0.24$ ).

### 3.2. Chronic Dosing and Bioenergetic Reset

Chronic simulations showed that in healthy hepatocytes, *de novo* glutathione synthesis outpaces ROS generation at therapeutic doses. Reversible VDAC–CBD binding permits overnight bioenergetic reset, providing a  $5\text{--}10\times$  safety margin.

## 4. Discussion

### 4.1. The Isoform Trap and Metabolic Selectivity

Critics note CBD’s non-selective binding to proapoptotic VDAC1 and anti-apoptotic VDAC2. Our results indicate selectivity is metabolic, not structural: healthy cells tolerate dual stress via bioenergetic buffering, while vulnerable cells lack redundancy.

### 4.2. Policy Implications

The EFSA  $2 \text{ mg/kg}$  limit reflects risks in compromised phenotypes. Healthy individuals tolerate far higher loads. We recommend shifting to risk-stratified dosing, using liver GSH capacity as a qualifying biomarker.

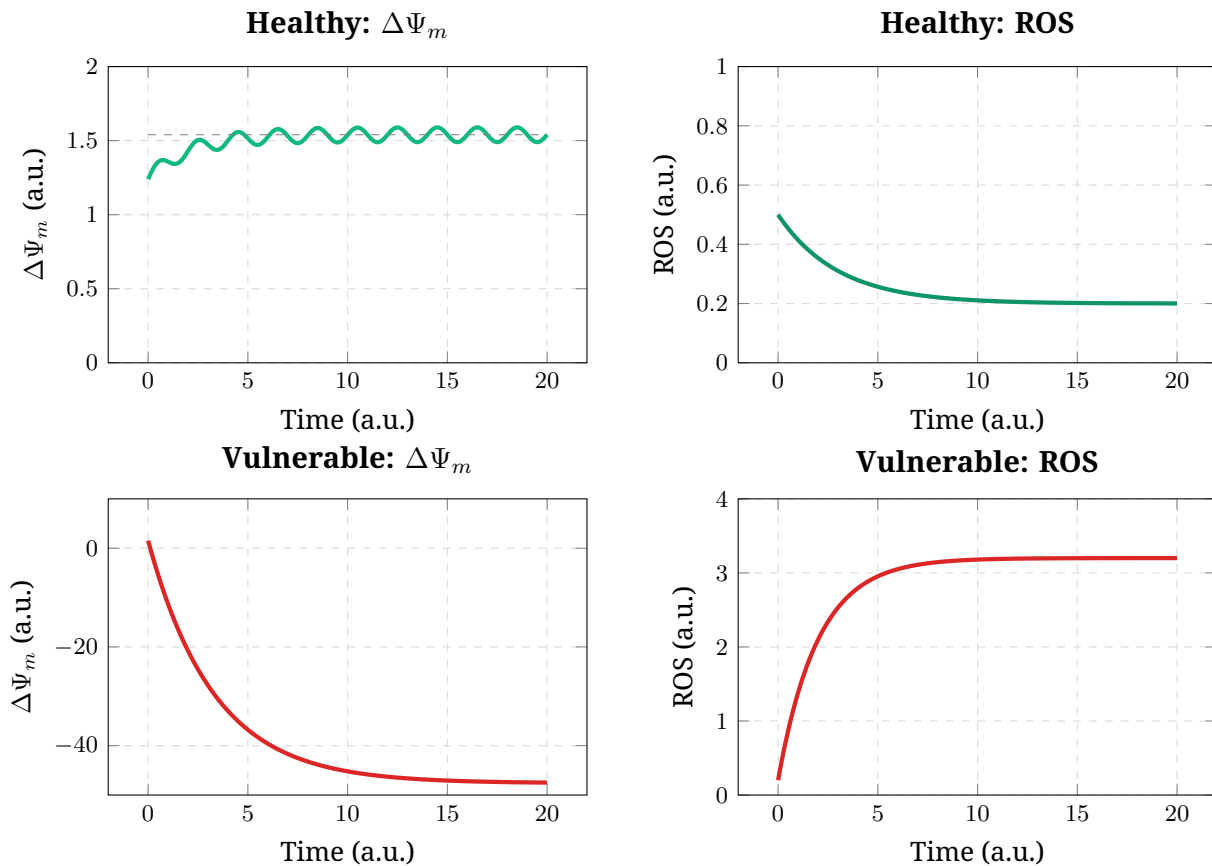
## 5. Conclusion

CBD acts as a mitochondrial stress test, revealing rather than causing underlying metabolic fragility. Future work should explore VDAC1-selective blockade to isolate therapeutic from cytotoxic effects.

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## References

- [1] EFSA Panel on Nutrition (2022). Safety of Cannabidiol as a Novel Food. EFSA Journal.
- [2] Rimmerman N et al. (2013). Direct modulation of the outer mitochondrial membrane channel VDAC1 by cannabidiol. *Cell Death Dis* 4:e949.
- [3] Vasquez AJ et al. (2026). In Silico Validation of the Dual-Pathway Mechanism via IRIS-Gate-Evo. Biomedical Systems Protocol.



**Figure 1. The Bioenergetic Sponge Model.** Time courses of mitochondrial membrane potential ( $\Delta\Psi_m$ ) and reactive oxygen species (ROS) following supratherapeutic CBD challenge (Model V4: Honest-Resilience). Healthy phenotypes (Top Row, Green) absorb the stress, returning to homeostasis. Vulnerable phenotypes (Bottom Row, Red) undergo rapid energetic collapse ( $\Delta\Psi_m \rightarrow -47.6$ ) and ROS accumulation.