

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

Anthony J. Vasquez Sr.

Department of Horticulture, Delaware Valley University
Temple of Two Research Group

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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 pro-apoptotic 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 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.

References

- [1] EFSA Panel on Nutrition (2022). Safety of Cannabidiol as a Novel Food. EFSA Journal.
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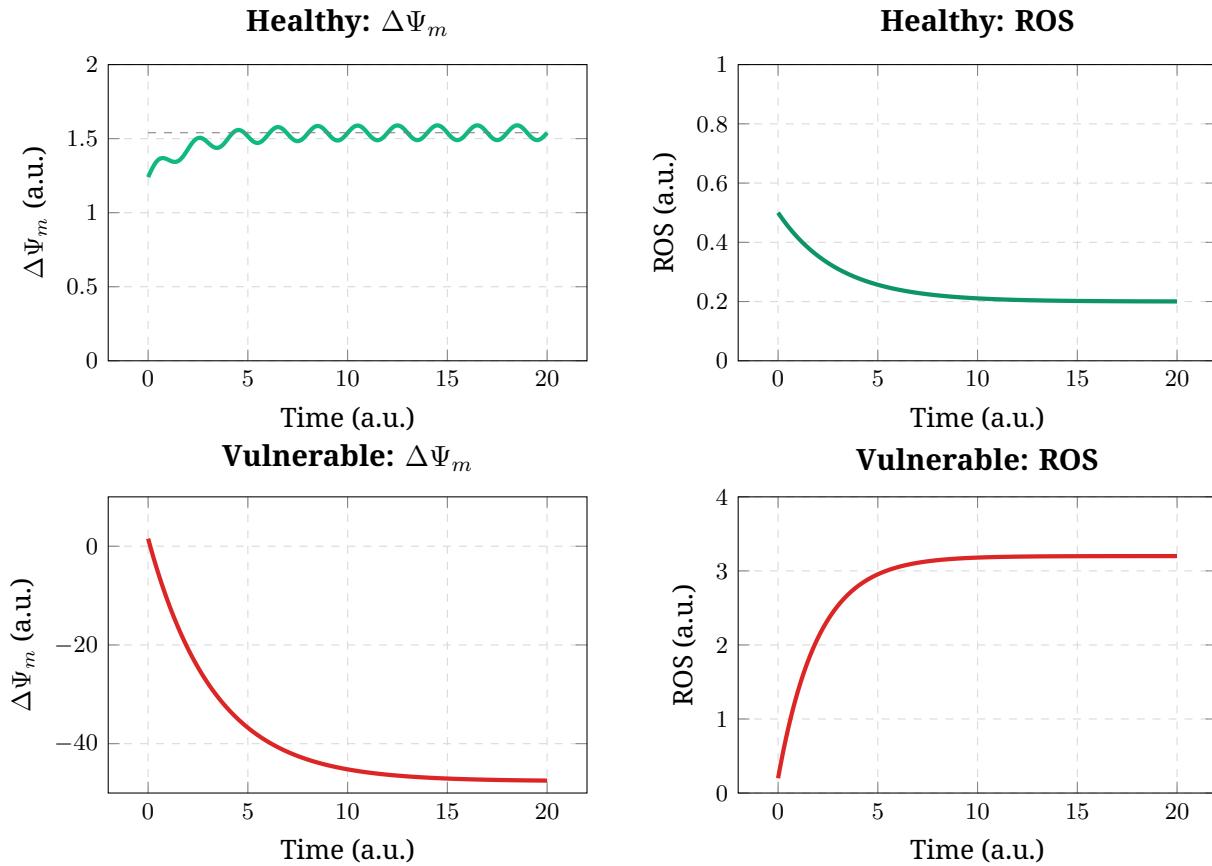


Figure 1. The Bioenergetic Sponge Model. Time courses of mitochondrial membrane potential ($\Delta\Psi_m$) and reactive oxygen species (ROS) following supratherapeutic CBD challenge (Model V4: Honest-Resilience). Healthy phenotypes (Top Row, Green) absorb the stress, returning to homeostasis. Vulnerable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