



Sciences' Plant-inspired Parkinson's Drugs



OTCQB:GBLX

Corporate Overview

Plant-Inspired Biotech Developing Prescription Drugs

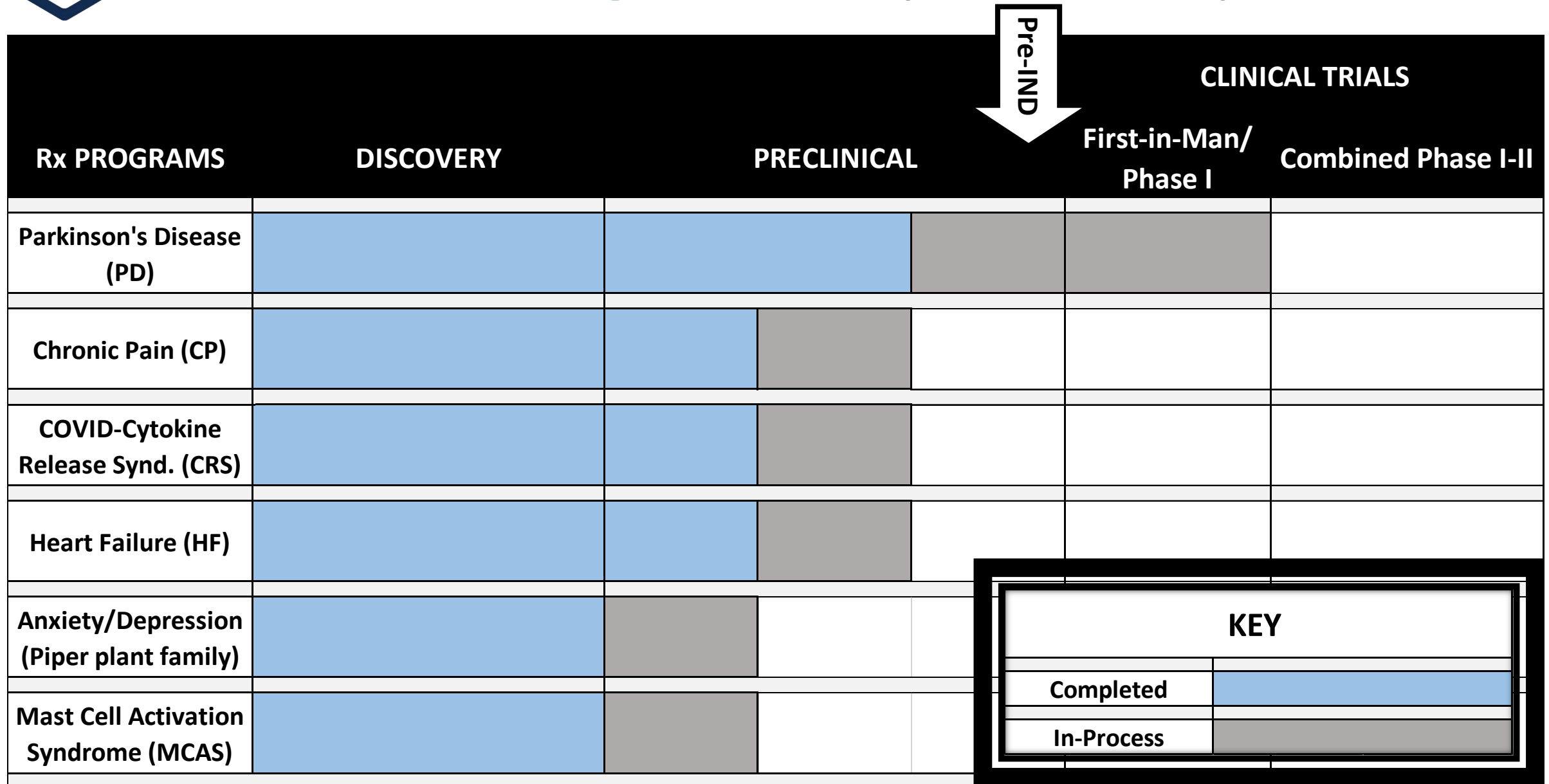
Drug Development Pipeline: Preparing lead candidate in PD for First-in-Human Trial

- Parkinson's Disease (PD): Patent issued; Preparing for First-in-Human Q4 2023
- Chronic Pain (CP): Patent issued; Preclinical study on-going at the NRC Canada
- COVID-Cytokine Release Syndrome (CRS): Patent filed; Preclinical study at Michigan State Univ.
- Heart Disease (HD): Patent issued; Proof-of-concept obtained at the University of Hawaii
- Anxiety (ANX): Patent filed; Preclinical study on-going at the NRC Canada

Discovery Program: Intellectual Property Portfolio covers >60 serious health conditions

- 6 US & 3 Foreign Patents Issued; 18 US & 49 Foreign Patents-Pending
- Proprietary Drug Discovery Platform – PhAROS™ Drug Discovery Engine
- Natural Products Research Combining Traditional Medical Systems and AI/Machine Learning

GbSciences' Drug Development Pipeline





Identification of minimum essential therapeutic mixtures from Cannabis plant extracts by screening in cell and animal models of Parkinson's disease

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Sciences' Drug Discovery Process

PhAROS

PhAROS™ Drug Discovery Platform
Data Analytics & Machine Learning

HTS

High Throughput Screening System
Disease-specific cell & animal models

MEM

Plant-inspired, Minimum Essential Mixtures
Synthetic cannabinoid API & IP (comp and use)

Best of Both = Plant-Inspired Medicines



Whole Plant Medicines

- 1000's of years of use in TMS
- Multiple Active Ingredients
- Multiple low affinity ligands & \geq one disease-related target
- Plant Sourcing Varied
- Difficult to achieve strict cGMP manufacturing standards
- Often nutraceutical products without US FDA premarket safety & efficacy data

Single Active Ingredient Drugs

- US FDA Friendly
- Single Active Ingredient
- One high affinity ligand and one disease-specific target
- API Manufacturing Consistent
- Manufactured to strict cGMP standards
- US FDA approval process ensures premarket review of safety & efficacy data

Plant-Inspired Minimum Essential Mixtures



1. Reduced Number of Compounds

- Sequential Screening Preserves Molecular Synergies in Plant Extracts
- 3 Active Pharmaceutical Ingredients (API) in each Minimum Essential Mixture
- Manufactured under cGMP using synthetic API (homologs of plant compounds)

2. Mechanisms of Action

- More complete model of biological targets regulating a biological disorder
- Not one drug = one target approach
- More complex, but not unknowable

3. Proprietary Oral Delivery Methods

- Increased bioavailability
- Increased patient compliance



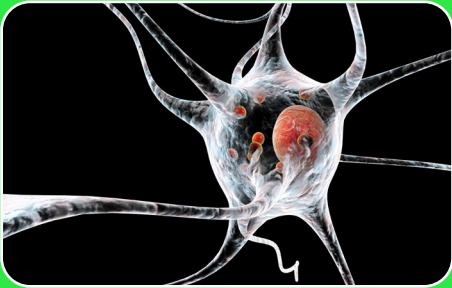
Gb Sciences' Parkinson's disease MEM™

Parkinson's disease: Multi-factorial Disorder



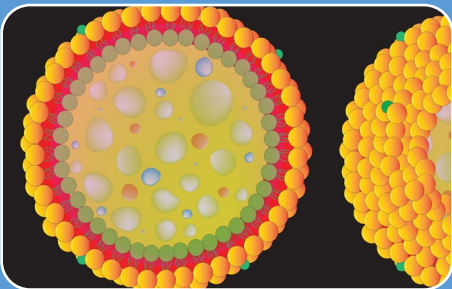
Mitochondrial Dysfunction

- Dysregulated Calcium Levels + Electron Transport Chain
- Increased ROS Contribute to Neuronal Cell Damage & Death



α -Synuclein Protein Misfolding & Lewy Bodies

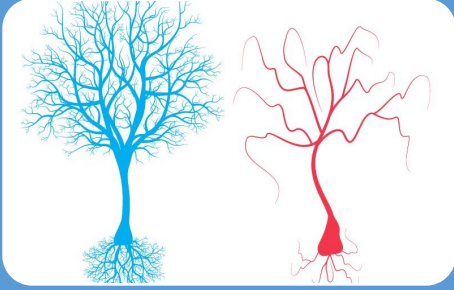
- Hallmark Features in Pathology
- Contribute to Damage & Death of Dopaminergic Neurons



Lysosomal Dysfunction

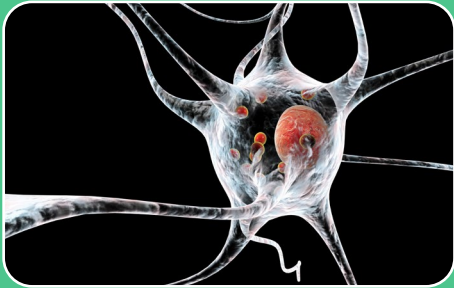
- Not clearing senescent mitochondria & misfolded proteins
- Interfering with synaptic transfer of neurotransmitters?

Parkinson's disease: Multi-factorial Disorder



Neuro-Inflammation

- Contributes to PD pathology: ie, neuropsychiatric & gut health
- Either a cause or an effect of PD disease progression



Death of Dopaminergic Neurons

- Hallmark Feature in Pathology (substantia nigra region)
- Reduced Dopamine Levels related to PD Symptoms



Motor & Non-Motor Symptoms

- Motor: Tremor, Stiffness, Slowness of Movement
- Non-Motor: Sleep, Swallowing, Digestion, Neuropsychiatric

Parkinson's MEM: Mechanisms of Action

Potential Role of Cannabis-based Ingredients in PD therapeutics



1. Cellular Level: Mitochondrial Dysfunction & Reactive Oxygen Damage

- Multiple cannabinoids (Cb's) are Anti-Oxidants (*Hampson et al., 2000*)
- Cb's help mitochondrial dysfunction, oxidative stress & neuroinflammation (*Mani et al. 2021*)
- CBD/TRP channel activation restores calcium dysregulation in mitochondria (*Hong et al., 2020*)

2. Systems Level: Desensitization of Dopamine (DA) Response in PD

- Cb's help alleviate desensitization of DAergic in PD (*More & Choi, 2015*)
- High CB1/CB2 & TRPV1 levels in midbrain (Basal Ganglia, globus pallidus & substantia nigra)
- ECB neuromodulation: DAergic, glutamatergic & GABAergic (*Patricio et al., 2020*)
- ECB Retrograde Signaling at synapse for inhibitory regulation of neurotransmitter release

3. Systems Level: Death of Dopaminergic Neurons (DAergic)

- Death of DAergic neurons in substantia nigra (*Gonzalez-Rodriguez et al., 2020*)
- Cb = neuroprotectants as anti-oxidants, calcium reg. & anti-inflammatory (*Patricio et al., 2020*)

4. Systems Level: Motor Symptoms

- CB Receptors & Cb levels high in Basal Ganglia regions (*Gonzalez-Rodriguez et al., 2020*)
- Slowness of movement in 6-OHDA model (*Feng et al., 2014, Benvenutti et al., 2018*)
- Tremor & Rigidity (*new data to support*)



Sciences Parkinson's Disease MEM™ Screens

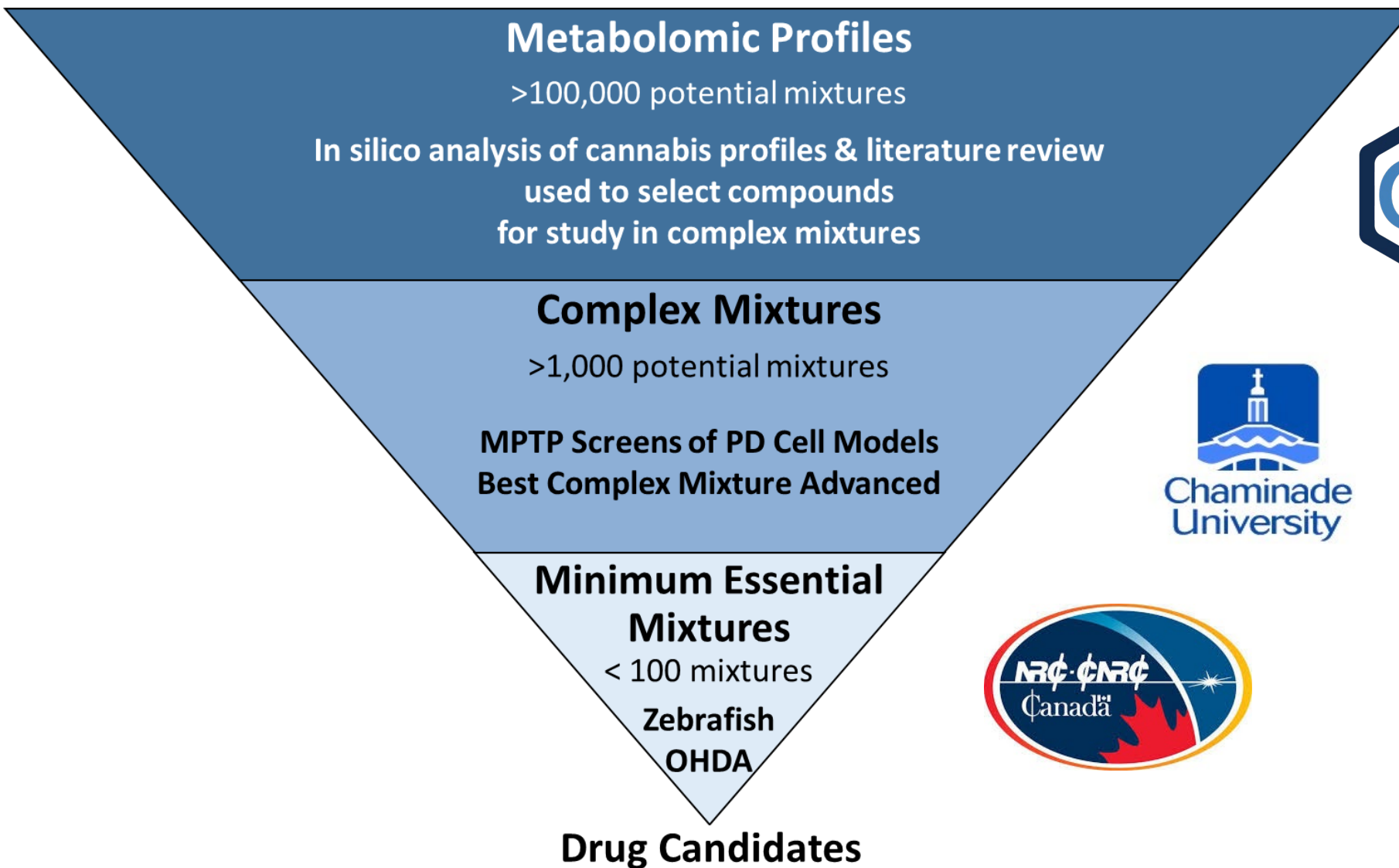


Figure 1. Reducing Complexity Identifies Minimal Essential Mixtures of Compounds for Parkinsonian Movement Disorders

Parkinson's MEM: Screens & Mech of Action



DAergic Neuron Assays

Mitochondrial Effects

- N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)
- Taken into cells through dopamine transport system (DAergic neurons)
- MPTP cleaved by MOA (intracellular) to MPP⁺ poisons the mitochondrial electron transport chain (>ROS/RNS)

Dopamine Secretion

- PD = impaired DA release
- Measure % increase in dopamine secretion relative to control

Initial Complex Mixture Results

In silico screening of Cannabis metabolomic profiles

- 11 cannabinoids & 19 terpenes measured per chemovar
- Desired profiles based on *in silico* data analytics & literature review (neuroinflammation, dopamine release, anti-oxidants, etc.)

Complex Mixture screening in DAergic neurons

- Tested >1000 complex mixtures (9 to 12 compounds in each)
- Rank ordered complex mixtures based on cell assay performance
- Chose MIX 1 (best performing complex mixture) for further study

MIX-1 Complex mixture to be optimized for MEM

5 Cannabinoids: 2 Major (CBD & CBN) + 3 Minor (CBC, CBG, CBDV)

5 Terpenes: D-limonene, linalool, t-nerolidol, a-pinene & phytol a

MPTP: Dose Response of Individual Cannabinoids

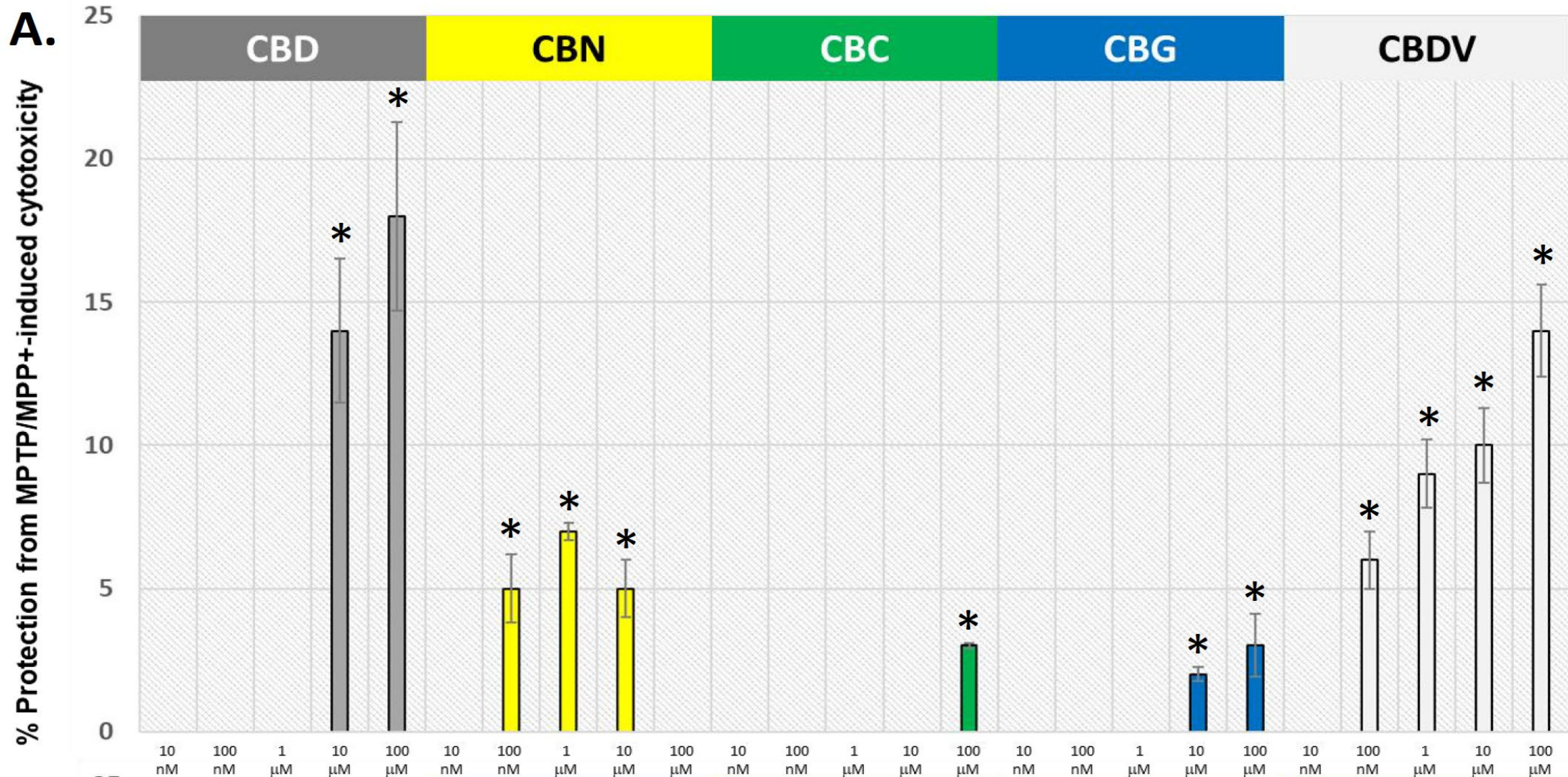


Figure 2. Tested the performance of components in MIX 1 separately. For the MPTP/MPP assay, the effectiveness is presented as the % protection from MPTP/MPP cell death evaluated based on the MTT cell viability assay, where the experimental value is normalized relative to the vehicle control.



MPTP: Dose Response of Individual Terpenes

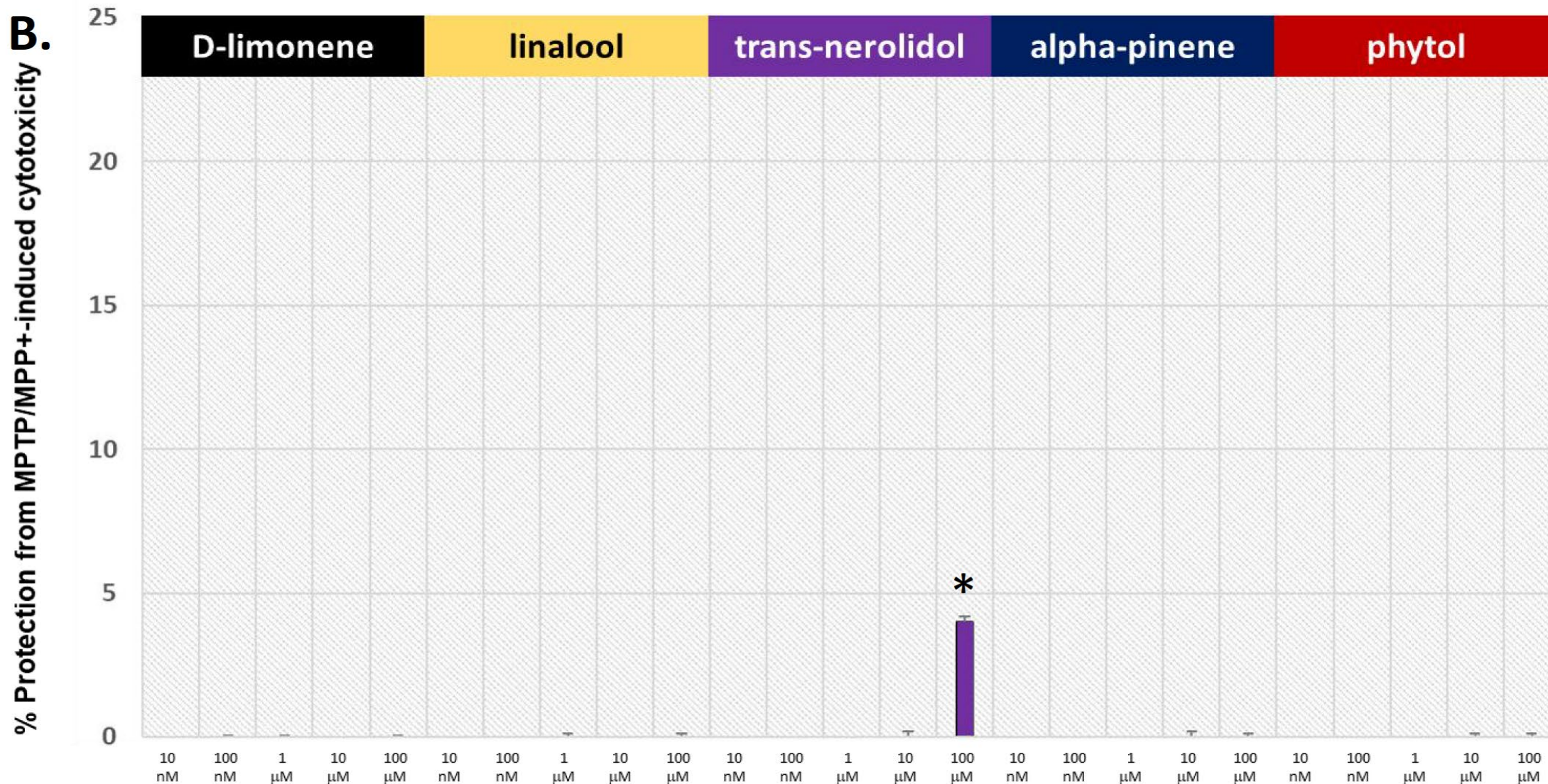
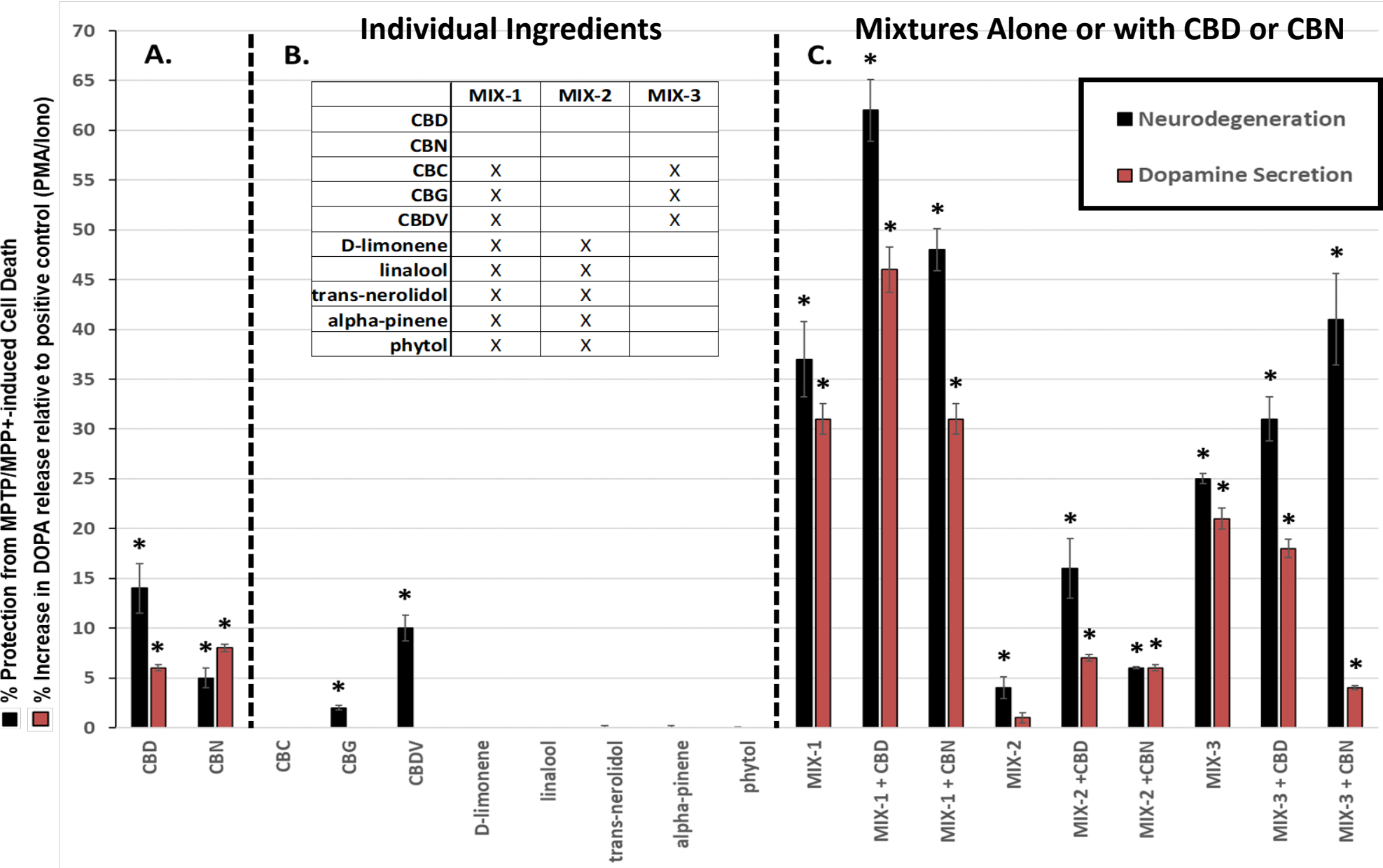


Figure 3. Tested the performance of components in MIX 1 separately. For the MPTP/MPP assay, the effectiveness is presented as the % protection from MPTP/MPP cell death evaluated based on the MTT cell viability assay, where the experimental value is normalized relative to the vehicle control.

Cannabinoid Contribution to Mix Greater Than Terpenes



Parkinson's MEM: Screens & Mech of Action



DAergic Neuron Assays

Mitochondrial Effects

- N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)
- Taken into cells through dopamine transport system (DAergic neurons)
- MPTP cleaved by MOA (intracellular) to MPP+ poisons the mitochondrial electron transport chain (>ROS/RNS)

Dopamine Secretion

- PD = impaired DA secretion
- Measure % increase in dopamine secretion relative to control

Zebrafish Assays

Motor Symptoms

- 6-Hydroxydopamine (6-OHDA) = a neurotoxic synthetic dopamine which selectively causes death in dopaminergic neurons

Slowness of Movement

- Total distance traveled
- Center point measurements
- Standard assay=gross movement

Tremor & Rigidity

- Novel phenotype
- Pixel-wise measurements
- Quality of movement



6-OHDA Targets Dopamine-Production

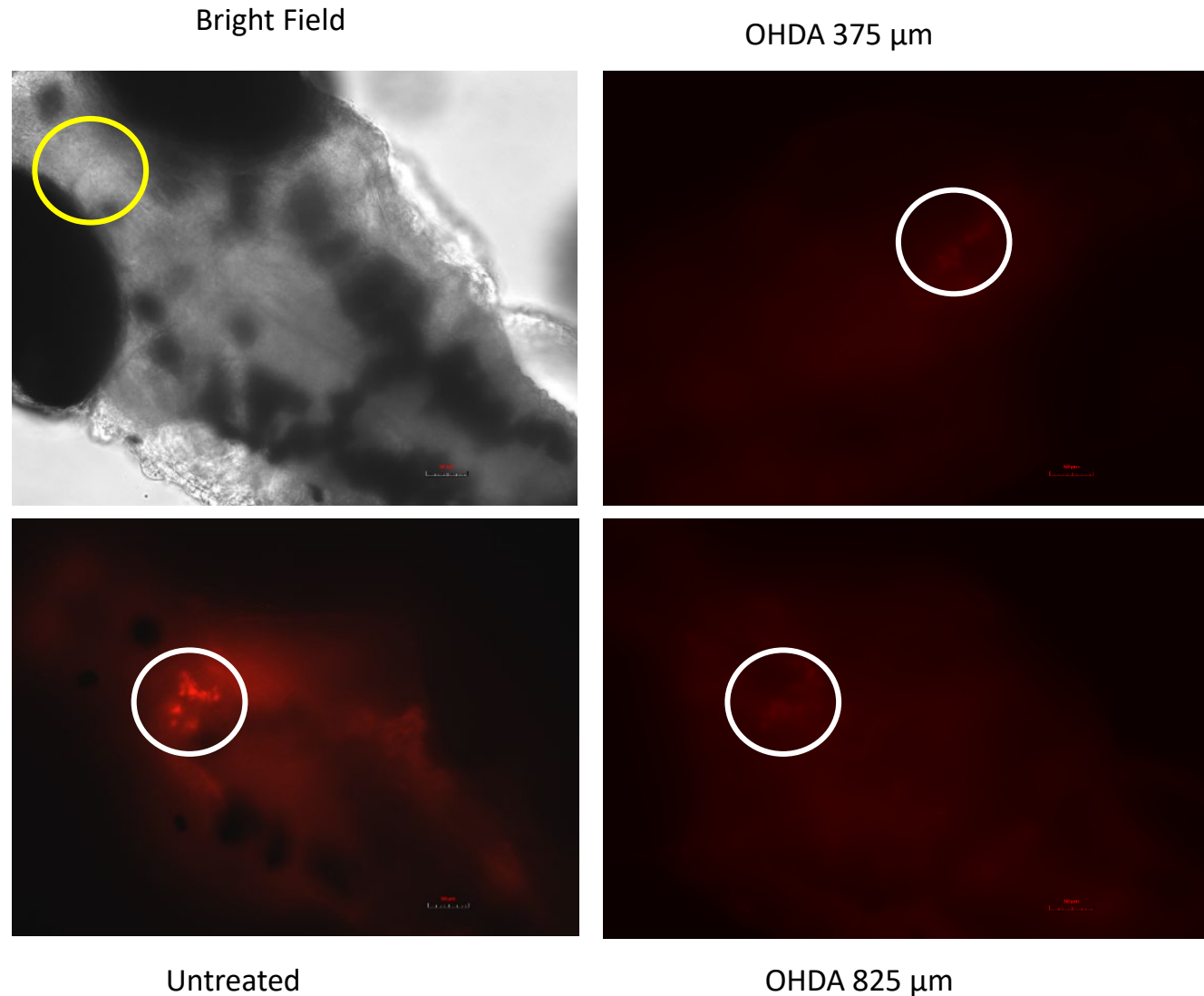


Figure 5. Immunohistochemistry of OHDA 48-120hpf treated larvae. Anti-Tyrosine Hydroxylase (Anti-TH) antibody at a 1:500 dilution). Reduced expression of dopamine linked-biomarker evident after 72 hrs of exposure to OHDA at stated concentrations. Similar pattern using cell-death markers.



Movement Studies: Distance Traveled vs 'Tremor'



Motor Symptoms

6-Hydroxydopamine (**6-OHDA**) = neurotoxic synthetic dopamine which selectively kills DAergic neurons

Slowness of Movement

- Total distance traveled
- Center point measurements
- Standard assay=gross movement

Tremor & Rigidity

- Novel phenotype
- % Pixel-change measurements
- Quality of movement

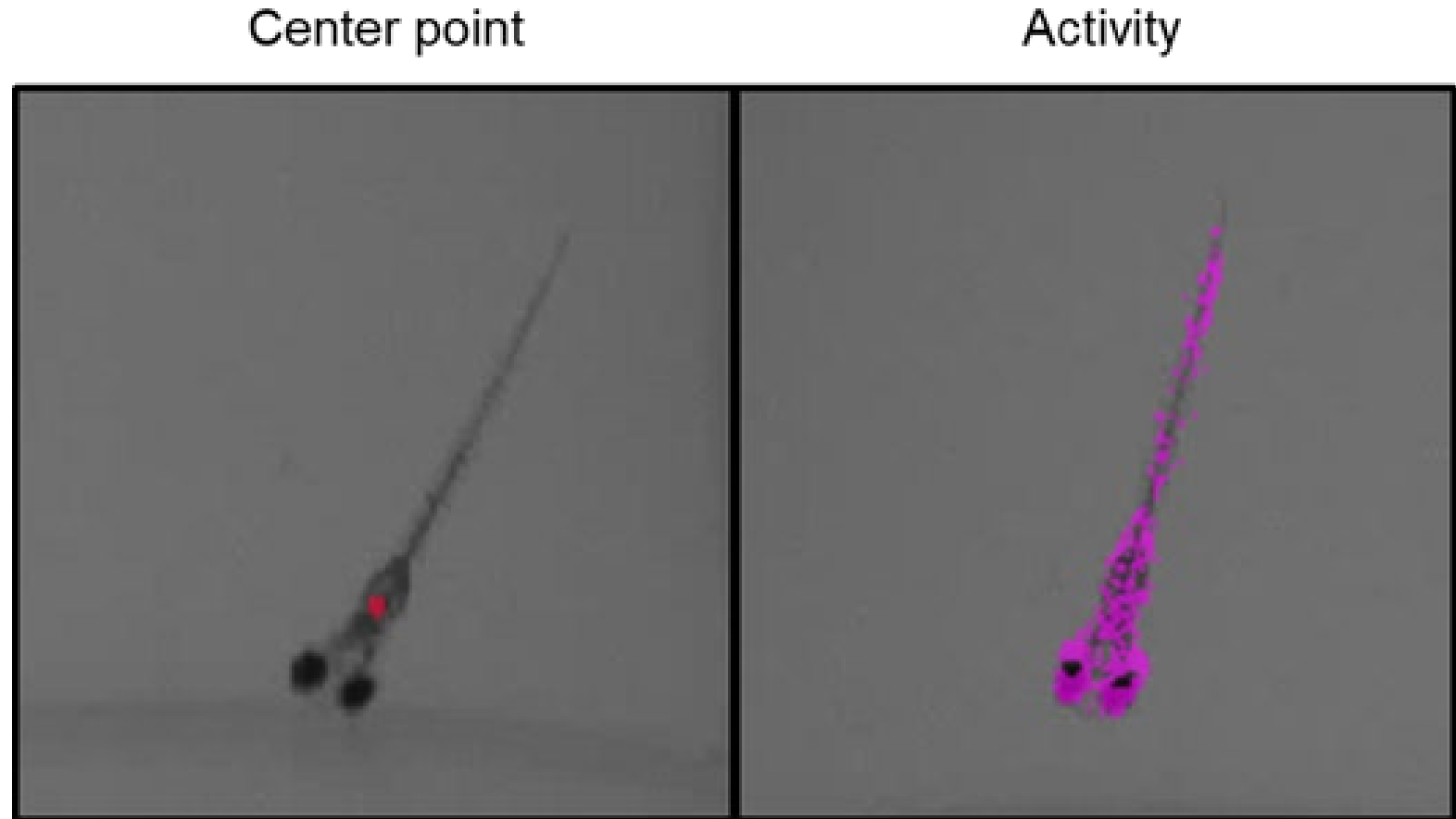


Figure 6. Measuring Motor Symptoms. Center point analyses were used to calculate the Total Distance Traveled for gross movement measurements. Whereas, Activity was measured on a % pixel-change basis for determinations of quality of movement including 'tremor-like' behavior. The % pixel-change measurements were translated into Activity states. Both the frequency of changing between Activity States and the Duration in the (non-tremor/'on') Activity States were reported.

OHDA Model of PD-like Motor Symptoms in Zebrafish

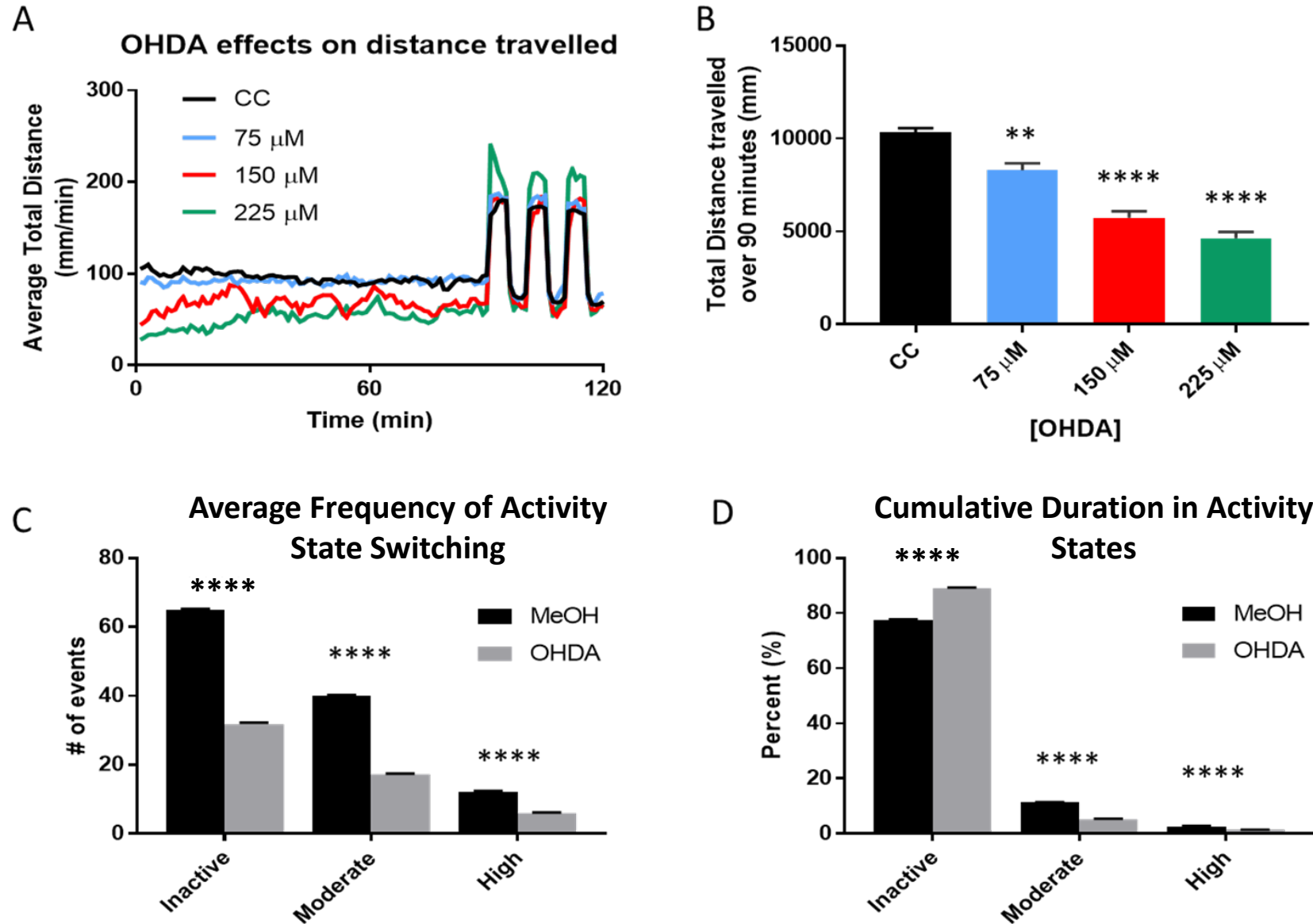


Figure 7. Validation of the larval zebrafish OHDA model. Behavioral profiles of total distance traveled (60 second bins) following OHDA exposure from 48-120 hpf. B - Total distance travelled during the first 90 minutes in the light following OHDA exposure from 48-120 hpf. Advanced activity analytics (C and D) of Average Frequency of switching between activity states (C) and the nested Cumulative duration in each activity state (D). ** = $p < 0.01$ **** = $p < 0.0001$. One way ANOVA with Dunnett's multiple comparisons test (A) and Student's T-test, two-tailed, unmatched for C and D.



Three Equimolar MEM™ Reduced PD-like Symptoms

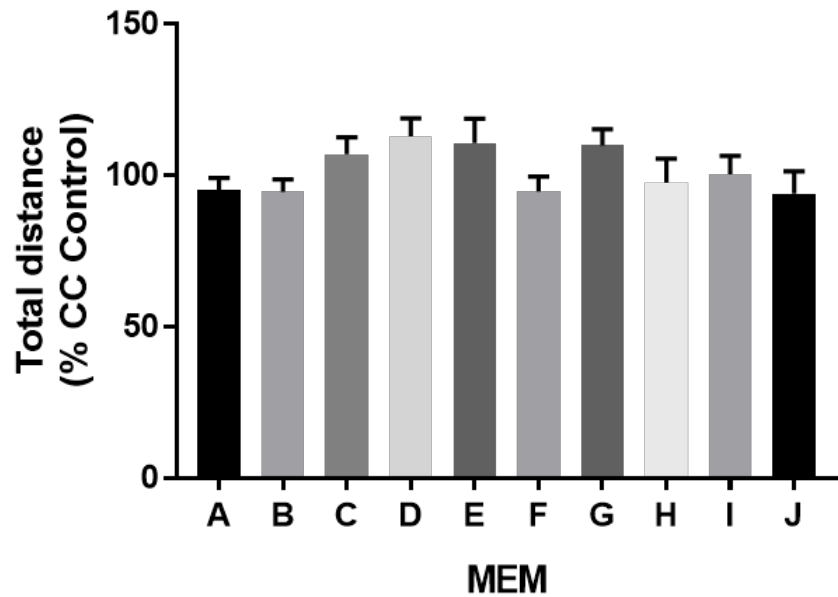


A

	MEM A	MEM B	MEM C	MEM D	MEM E	MEM F	MEM G	MEM H	MEM I	MEM J
1st	CBC	CBC	CBC	CBC	CBC	CBC	CBD	CBD	CBD	CBDV
2nd	CBD	CBD	CBD	CBDV	CBDV	CBG	CBDV	CBDV	CBG	CBG
3rd	CBDV	CBG	CBN	CBG	CBN	CBN	CBG	CBN	CBN	CBN

B

MEM vs Control



C

MEM+OHDA vs OHDA

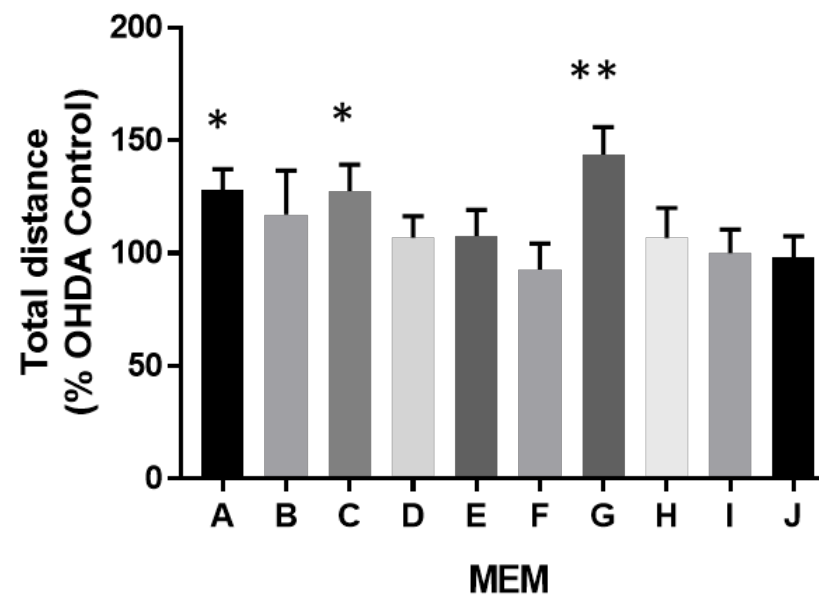


Figure 8. Minimal Essential Mixtures (MEM) alleviate OHDA mediated hypoactivity. A – Five cannabinoids were used to create the 10 possible 3 component equimolar mixtures. Each of the 0.5uM MEM was assessed for its ability modify total distance travelled of B - Carrier Control (CC) or C – 150uM OHDA. Data is normalized to either CC (B) or OHDA (C).
* = $p < 0.05$, ** $p < 0.01$.



Three Equimolar MEMTM Reduced PD-like Symptoms

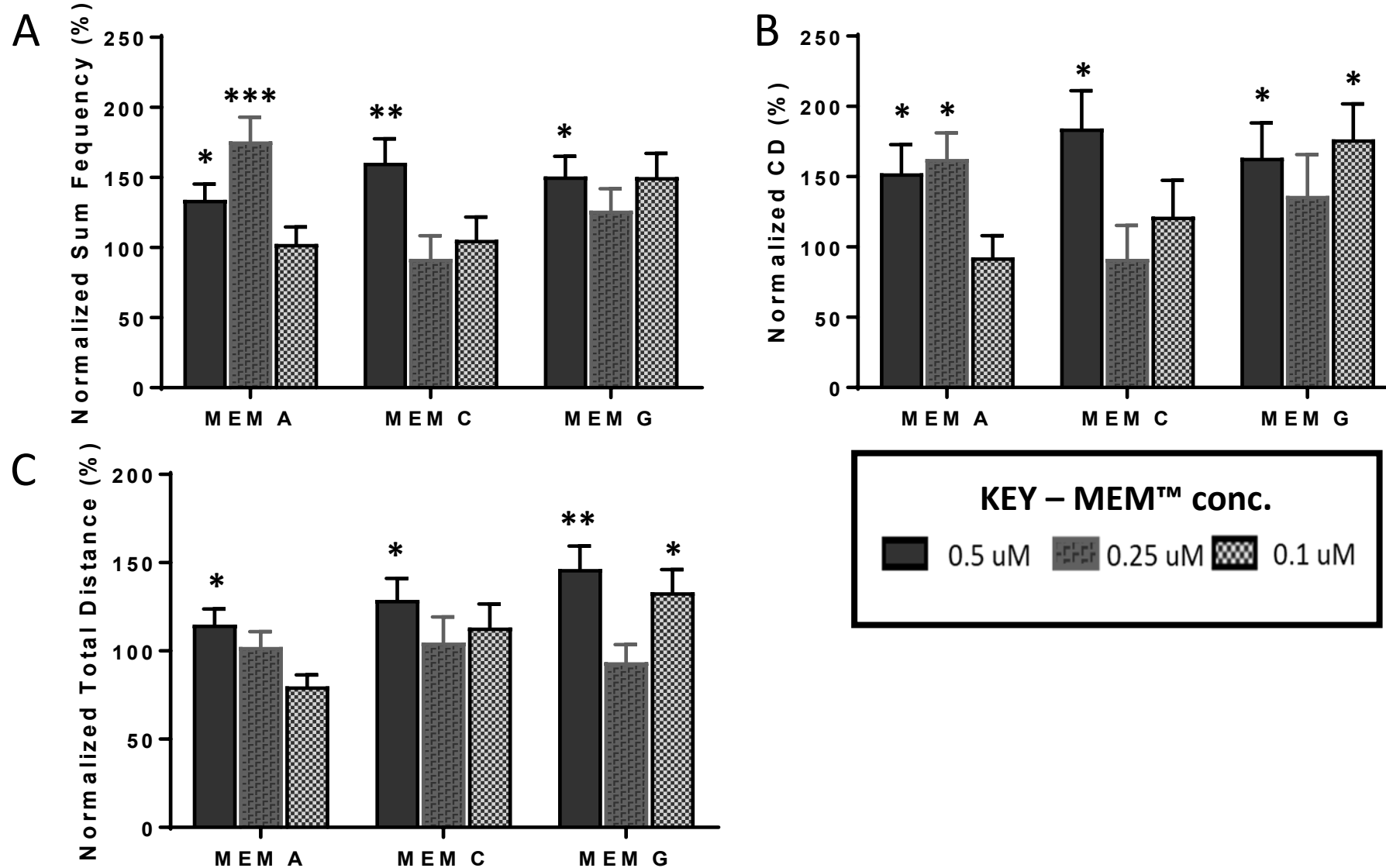


Figure 9. Equimolar MEMs alleviate both OHDA mediated frequency and cumulative duration deficits. Activity metrics of Average Frequency (A), High + Medium Cumulative Duration (B) and Total Distance (C) for equimolar MEMs at 0.5, 0.25 and 0.1uM. +150uM OHDA vs 150 uM OHDA. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.





Optimized Cb-Ratio MEM™ Outperformed Equimolar MEM™

	166.6 nM CBD			83.3 nM CBD			16.6 nM CBD		
MIX A	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV
166.6 nM CBC	* / *	*** / *	0	* / *	0	0	* /	0	0
83.3 nM CBC	0	0	0	0	*** / *	N/A	0	N/A	N/A
16.6 nM CBC	** /	0	** /	0	N/A	N/A	0	N/A	0
MIX C	166.6 nM CBN	83.3 nM CBN	16.6 nM CBN	166.6 nM CBN	83.3 nM CBN	16.6 nM CBN	166.6 nM CBN	83.3 nM CBN	16.6 nM CBN
166.6 nM CBC	** / *	0	* /	0	0	0	0	0	0
83.3 nM CBC	0	*** / *	0	0	0	N/A	** /	N/A	N/A
16.6 nM CBC	0	* /	** /	0	N/A	N/A	0	N/A	0
MIX G	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV	166.6 nM CBDV	83.3 nM CBDV	16.6 nM CBDV
166.6 nM CBG	* / *	* /	0	* / *	0	0	*	*** / *	* /
83.3 nM CBG	0	** / *	/-	*** / *	0	N/A	0	N/A	N/A
16.6 nM CBG	0	0	0	0	N/A	N/A	0	N/A	/ *

Figure 10. Twenty-two Cannabinoid-Ratio Optimized MEM™ Reduced PD-motor Symptoms. Concentrations of the three cannabinoids in each MEM results cell are shown starting with CBD (labeled in the top row). The second cannabinoid/concentration for each ratio result is in the first column of the table, and the last cannabinoid/concentration is above the cell in the row containing the label of the original equimolar ratio formula. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ on either side of the “/” represent the level of statistical significance in change in the Frequency of Activity State Change metric (right-side)/Cumulative Duration metric (left-side) of zebrafish exposed to the MEM + OHDA versus the OHDA-alone group. Zeroes represent no statistically-significant change in activity, “-” indicates a further reduction or increase in PD-like symptoms.



Optimized MEM™ Reduced PD-like Motor Symptoms

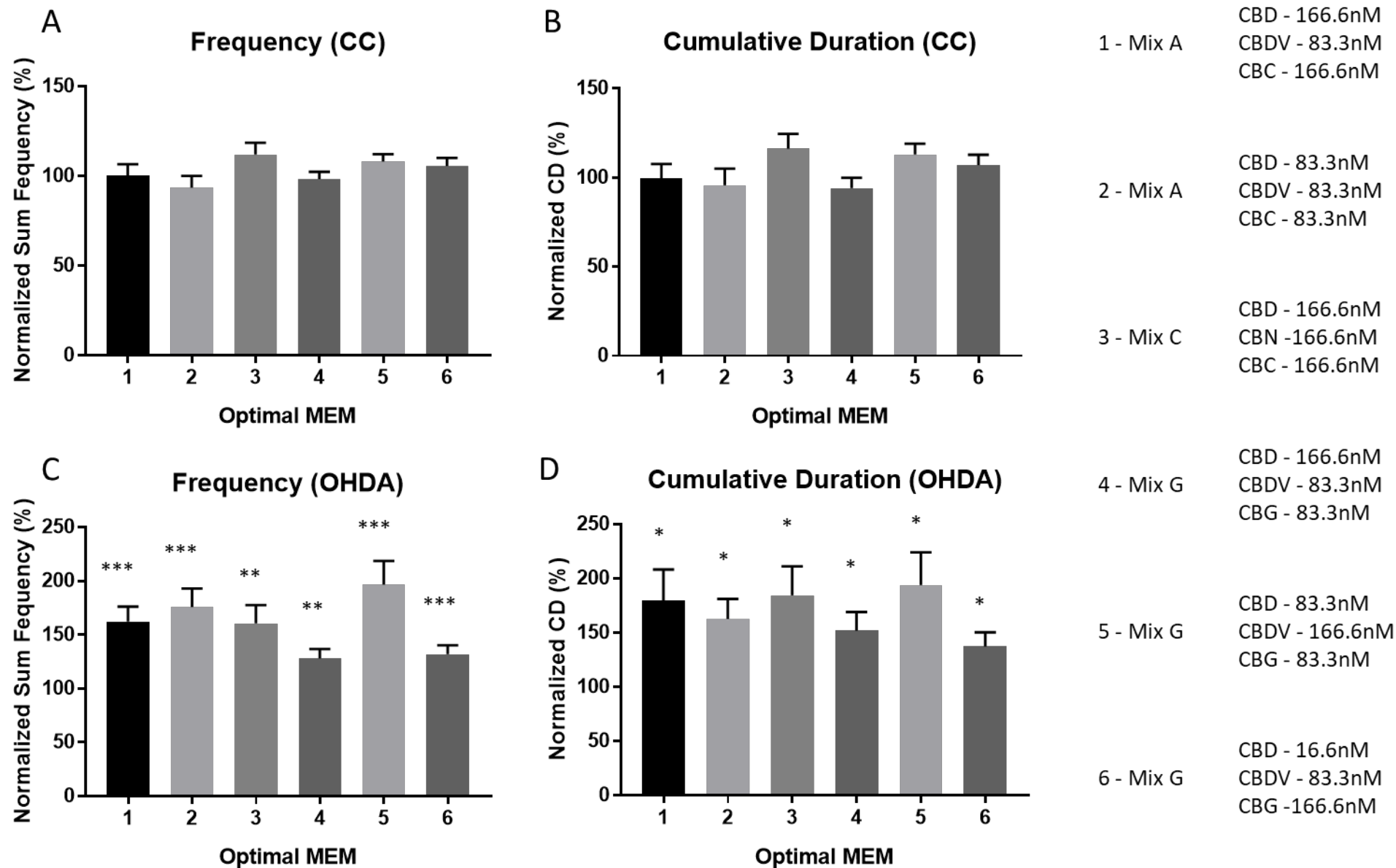


Figure 11. Optimal MEM™ ratios alleviate both OHDA -mediated activity state frequency of shifting and cumulative duration deficits. Activity metrics of Average Frequency (A, C) and High + Medium Cumulative Duration (B, D). Optimal MEM vs methanol carrier control (A and B), and Optimal MEM+150uM OHDA vs 150 uM OHDA (C and D). * p < 0.05, ** p < 0.01, *** p < 0.001.



Conclusions: Significant PD-Motor Symptom Reduction

PD MEM™ in Parkinson's Animal Study—NRC Canada

- Zebrafish model of Parkinson's Disease-72 hr OHDA Exposure
 - Restored overall movement levels (measured based on total distance moved)
 - Reduced “resting tremor”(measured frequency & duration of shifts in activity states)
 - Normal startle response (Light/Dark)
- Statistically Significant Reduction of PD-like Motor Symptoms
 - 3 of 10 Equimolar MEM™
 - 22 of 63 Cannabinoid-Ratio Controlled MEM™
 - 5 outperformed the other MEM™
 - 3 selected for formulation and ADMET testing as clinical trial prototypes



Results suggest Mechanism of Action of MEM



1. Cellular Level: Mitochondrial Dysfunction

- Cannabinoids protected against MPTP/MPP+
- Mixtures enhanced protection against MPTP/MPP+

2. Cellular Level: Dopamine (DA) Release

- Cannabinoids increased dopamine release
- Mixtures enhanced dopamine release

3. Systems Level: Death of Dopaminergic Neurons (DAergic)

- Anti-TH visualization in the midbrain of the zebrafish confirms
- Cannabinoids appear to be neuroprotectants (6-OHDA)

4. Systems Level: 6-OHDA Induced PD-Motor Symptoms

- Slowness of movement = Mixtures improved total distance traveled
- Tremor = Mixtures increased “on” periods (no ‘tremor’)



Summary: Plant-Inspired Strategy

Formulations: Minimum Essential Mixtures (MEM™)

- Whole plant efficacy retained, yet manufacturing efficiencies of single ingredients
- MEM™ retain molecular synergies of complex (>100 compounds) plant extracts
- Optimized to 3 compounds per MEM™

Active Ingredients: Synthetic Homologues of Plant Compounds

- Synthetic homologues are identical in structure to plant compounds
- Regulatory & supply chain advantages over plant-based compounds
- Manufactured under current Good Manufacturing Practices (cGMP)

Delivery Modes: Oral Routes

- Improved bioavailability
- Increased patient compliance
- Oral dissolving tablets (ODT), oral nanoparticles, oral thin film, gel capsules

PD Clinical: Orally Disintegrating Tablets (ODT)

Zydis™ Orally Disintegrating Tablets (ODT)

- Unique, freeze-dried oral solid dosage
- Instant oral dispersion – typically less than 3 seconds

Parkinson's MEM™ in Zydis™ ODT

- Convenient dosing solution for Parkinson's patients
- Greater than 50% of Parkinson's patients have swallowing problems

Clinical Advantages

- Improved bioavailability
- Increased patient compliance
- Rapid onset through buccal/sublingual absorption

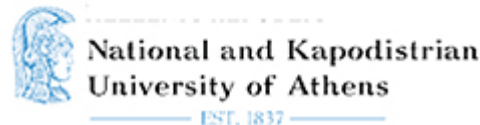


Zydis™ Orally Disintegrating Tablets (ODT)

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ANDREA SMALL-HOWARD, PHD, MBA

Chairman of the Scientific Advisory Board, Chief Science Officer and President of GB Sciences/GBS Global Biopharma

Dr. Andrea Small-Howard has more than 20 years of scientific research experience; as well as executive experience in the biopharmaceutical industry supervising research & development, manufacturing, and quality control divisions in the US and China.



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Dr. Zoltan Mari graduated first in his medical school class in Hungary before completing a post-doctoral fellowship in SUNY Downstate (Brooklyn, NY) on Parkinson disease (PD) animal models and electrophysiology.



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Dr. Alex Stokes has an impeccable pedigree from a twenty-five career in research and development. He has an excellent track record of cutting-edge research.

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