

## Theme: Pre-clinical Research and Mechanisms of Disease

### Targeting Depression: Can phytocannabinoids modulate neuroinflammation and behavior despair?

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#### Abstract:

Depression is a widespread mental health disorder often caused by stress stimuli and neuroinflammation. Currently, treatment options remain limited, underscoring the need for further research. This study investigated six phytocannabinoids (pCBD), cannabichromene (CBC), cannabichromenic acid (CBCA), cannabidiol (CBD), cannabidivarin (CBDV), cannabigerol (CBG) and cannabinol (CBN), regarding their effect on cell viability and anti-inflammatory activity in mouse microglia cell line (BV-2). The three most promising pCBD were, then, administered to mice (55  $\mu\text{mol/kg}$ , i.p.) to evaluate their acute protective impact against behavioral despair, a hallmark of depression. The IC<sub>50</sub> ( $\mu\text{M}$ ) values found after the Alamar blue assay in BV-2 cells were 21.65 (CBC), >30 (CBCA), 17.85 (CBD), 28.08 (CBDV), 29.01 (CBG) and 22.68 (CBN). Anti-inflammatory properties of each pCBD (10  $\mu\text{M}$ ) were investigated on lipopolysaccharide (LPS)-stimulated BV-2 cells. Nitrite levels were quantified by Griess reaction, and iNOS and pro-IL1 $\beta$  were extracted from scraped cells and quantified by western blot. CBDV reduced IL1 $\beta$  ( $p=0.0223$ ), iNOS ( $p=0.0304$ ) and nitrites ( $p=0.0009$ ) while CBD reduced iNOS ( $p=0.0359$ ) compared to untreated cells. In non-LPS-stimulated BV-2 cells, any pCBD elevated IL1 $\beta$ , iNOS, or nitrite levels.

Based on the in vitro findings, CBD, CBDV and CBG were tested in vivo and compared with ketamine (positive control) or vehicle (negative control). In the Open Field Test, CBG increased the activity percentage in the central zone compared to negative ( $p=0.0202$ ) and positive ( $p=0.0159$ ) controls, suggesting an anxiolytic effect without impairing locomotion. In the Forced Swimming Test, CBG increased swimming ( $p=0.0468$ ) and reduced immobility ( $p=0.0159$ ) times compared to the negative control, indicating an antidepressant-like effect. CBD and CBDV showed no statistical differences compared to controls. These findings suggest CBG may hold therapeutic potential for anxiety and depressive disorders.

**Keywords:** Depression; Phytocannabinoids; Neuroinflammation; Behavior despair, preclinical studies.