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# Pharmacological data of cannabidiol- and cannabigerol-type phytocannabinoids acting on cannabinoid $CB_1$, $CB_2$ and $CB_1/CB_2$ heteromer receptors

Gemma Navarro [1], Katia Varani [2], Alejandro Lillo [3], Fabrizio Vincenzi [2], Rafael Rivas-Santisteban [4], Iu Raïch [4], Irene Reyes-Resina [4], Carlos Ferreiro-Vera [5], Pier Andrea Borea [6], Verónica Sánchez de Medina [5], Xavier Nadal [7], Rafael Franco [8]

Affiliations
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## Abstract

**Background:** Recent approved medicines whose active principles are $\Delta^9$Tetrahidrocannabinol ($\Delta^9$-THC) and/or cannabidiol (CBD) open novel perspectives for other phytocannabinoids also present in Cannabis sativa L. varieties. Furthermore, solid data on the potential benefits of acidic and varinic phytocannabinoids in a variety of diseases are already available. Mode of action of cannabigerol (CBG), cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), cannabidivarin (CBDV) and cannabigerivarin (CBGV) is, to the very least, partial.

**Hypothesis/purpose:** Cannabinoid $CB_1$ or $CB_2$ receptors, which belong to the G-protein-coupled receptor (GPCR) family, are important mediators of the action of those cannabinoids. Pure CBG, CBDA, CBGA, CBDV and CBGV from Cannabis sativa L. are differentially acting on $CB_1$ or $CB_2$ cannabinoid receptors.

**Study design:** Determination of the affinity of phytocannabinoids for cannabinoid receptors and functional assessment of effects promoted by these compounds when interacting with cannabinoid receptors.

**Methods:** A heterologous system expressing the human versions of $CB_1$ and/or $CB_2$ receptors was used. Binding to membranes was measured using radioligands and binding to living cells using a homogenous time resolved fluorescence resonance energy transfer (HTRF) assay. Four different functional outputs were assayed: determination of cAMP levels and of extracellular-signal-related-kinase phosphorylation, label-free dynamic mass redistribution (DMR) and ß-arrestin recruitment.

**Results:** Affinity of cannabinoids depend on the ligand of reference and may be different in membranes and in living cells. All tested phytocannabinoids have agonist-like behavior but behaved as inverse-agonists in the presence of selective receptor agonists. CBGV displayed enhanced potency in many of the functional outputs. However, the most interesting result was a biased signaling that correlated with differential affinity, i.e. the overall results suggest that the binding mode of each ligand leads to specific receptor conformations underlying biased signaling outputs.

**Conclusion:** Results here reported and the recent elucidation of the three-dimensional structure of $CB_1$ and $CB_2$ receptors help understanding the mechanism of action that might be protective and the molecular drug-receptor interactions underlying biased signaling.

**Keywords:** Biased signaling; Cytocrin; GPCR structure; Homogeneous binding; Phytocannabinoids; Radioligand binding.

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