## Modulation of Angiotensin II-Induced Cellular Hypertrophy by Cannflavin-C: Unveiling the Impact on Cytochrome P450s 1B1 and Arachidonic Acid Metabolites

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Cannflavin-C is a prenylated flavonoid found in Cannabis sativa that has been shown to have anti-inflammatory and analgesic properties. Currently there is no evidence to suggest that Cannflavin-C has any significant effects on the heart or cardiac hypertrophy. Cytochrome P450 1B1 (CYP1B1)-mediated metabolism of arachidonic acid (AA) into the cardiotoxic midchain hydroxyeico-satetraenoic acids (HETEs) contributes to the development of cardiac hypertrophy, a condition characterized by an increase in the size of cardiac cells. This investigation aimed to elucidate the effect of Cannflavin-C on Angiotensin II (Ang II)-induced cellular hypertrophy and its potential role in modulating AA metabolites. Cultured adult human ventricular cardiomyocytes cell line (AC16) were subjected to 100 nM Cannflavin-C in the presence and absence of 10 µM Ang II. Real-time polymerase chain reaction (PCR) was utilized for mRNA expression analysis related to cellular hypertrophic markers and CYPs, while Western blot analysis was used for quantifying CYPs protein levels. Ang II induced the gene expression of hypertrophic markers and increased cell surface area, both of which were mitigated by Cannflavin-C. Gene expression analysis revealed that Cannflavin-C downregulated CYP1B1 gene expression, protein levels, and activity measured by 7-methoxyresorufin O-deethylase (MROD). Arachidonic acid metabolite analysis using LC-MS/MS demonstrated that Ang II elevated midchain (R/S)-HETEs concentrations, a response attenuated by Cannflavin-C. This study provides novel insights into the potential of Cannflavin-C in modulating arachidonic acid metabolites and attenuating Ang II-induced cellular hypertrophy, highlighting its importance as a potential therapeutic agent for cardiac hypertrophy.

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