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# Inhibition of UDP-Glucuronosyltransferase Enzymes by Major Cannabinoids and Their Metabolites

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## Abstract

The UDP-glucuronosyltransferase (UGT) family of enzymes play a central role in the metabolism and detoxification of a wide range of endogenous and exogenous compounds. UGTs exhibit a high degree of structural similarity and display overlapping substrate specificity, often making estimations of potential drug-drug interactions difficult to fully elucidate. One such interaction yet to be examined may be occurring between UGTs and cannabinoids, as the legalization of recreational and medicinal cannabis and subsequent co-usage of cannabis and therapeutic drugs increases in the United States and internationally. In the present study, the inhibition potential of the major cannabinoids $\Delta^9$-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), as well as their major metabolites, was determined in microsomes isolated from HEK293 cells overexpressing individual recombinant UGTs and in microsomes from human liver and kidney specimens. The highest inhibition was seen by CBD against the glucuronidation activity of UGTs 1A9, 2B4, 1A6, and 2B7, with binding-corrected $IC_{50}$ values of 0.12 ± 0.020 μM, 0.22 ± 0.045 μM, 0.40 ± 0.10 μM, and 0.82 ± 0.15 μM, respectively. Strong inhibition of UGT1A9 was also demonstrated by THC and CBN, with binding-corrected $IC_{50}$ values of 0.45 ± 0.12 μM and 0.51 ± 0.063 μM, respectively. Strong inhibition of UGT2B7 was also observed for THC and CBN; no or weak inhibition was observed with cannabinoid metabolites. This inhibition of UGT activity suggests that in addition to playing an important role in drug-drug interactions, cannabinoid exposure may have important implications in patients with impaired hepatic or kidney function. SIGNIFICANCE STATEMENT: Major cannabinoids found in the plasma of cannabis users inhibit several UDP-glucuronosyltransferase (UGT) enzymes, including UGT1A6, UGT1A9, UGT2B4, and UGT2B7. This study is the first to show the potential of cannabinoids and their metabolites to inhibit all the major kidney UGTs as well as the two most abundant UGTs present in liver. This study suggests that as all three major kidney UGTs are inhibited by cannabinoids, greater drug-drug interaction effects might be observed from co-use of cannabinods and therapeutics that are cleared renally.



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