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Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review.

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Abstract

Exogenous cannabinoids are structurally and pharmacologically diverse compounds that are widely used. The purpose of this systematic review is to summarize the data characterizing the potential for these compounds to act as substrates, inhibitors, or inducers of human drug metabolizing enzymes, with the aim of clarifying the significance of these properties in clinical care and drug interactions. In vitro data were identified that characterize cytochrome P-450 (CYP-450) enzymes as potential significant contributors to the primary metabolism of several exogenous cannabinoids: tetrahydrocannabinol (THC; CYPs 2C9, 3A4); cannabidiol (CBD; CYPs 2C19, 3A4); cannabinol (CBN; CYPs 2C9, 3A4); JWH-018 (CYPs 1A2, 2C9); and AM2201 (CYPs 1A2, 2C9). CYP-450 enzymes may also contribute to the secondary metabolism of THC, and UDP-glucuronosyltransferases have been identified as capable of catalyzing both primary (CBD, CBN) and secondary (THC, JWH-018, JWH-073) cannabinoid metabolism. Clinical pharmacogenetic data further support CYP2C9 as a significant contributor to THC metabolism, and a pharmacokinetic interaction study using ketoconazole with oromucosal cannabis extract further supports CYP3A4 as a significant metabolic pathway for THC and CBD. However, the absence of interaction between CBD from oromucosal cannabis extract with omeprazole suggests a less significant role of CYP2C19 in CBD metabolism. Studies of THC, CBD, and CBN inhibition and induction of major human CYP-450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking. Smoked cannabis herb (marijuana) likely induces CYP1A2 mediated theophylline metabolism, although the role of cannabinoids specifically in eliciting this effect is questionable.

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