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.

Keywords
AM2201, cannabis, cannabidiol, dronabinol, drug interactions, JWH-018, JWH-073, tetrahydrocannabinol

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Introduction
Cannabinoids are structurally diverse chemicals capable of exerting a broad range of pharmacologic effects (Ashton, 2001; Ben Amar, 2006; ElSohly & Slade, 2005; Fattore & Fratta, 2011; Mehmedic et al., 2010; Pacher et al., 2006). Historically, the known cannabinoids were a group of related C21 terpenophenolic compounds and their biologic derivatives – the so-called “phytocannabinoids” – found in plants of the Cannabis genus, including Cannabis sativa, Cannabis indica, and Cannabis ruderalis. Today, the term “cannabinoid” is also used to refer to synthetic analogs of these compounds, many of which have no known natural source, as well as endogenous cannabinoid receptor ligands such as anandamide and 2-arachidonoylglycerol (ElSohly & Slade, 2005; Fattore & Fratta, 2011; Pacher et al., 2006).

Exogenous cannabinoids are widely consumed, in a variety of forms. Cannabinoid-rich preparations of cannabis, either in herb (i.e. marijuana) or resin form, are used by an estimated 2.6–5.0% of the world population (UNODC, 2012). Cannabinoid containing pharmaceutical products, either containing natural cannabis extracts (Sativex®, GW Pharmaceuticals) or the synthetic cannabinoids dronabinol ([−]-Δ²-tetrahydrocannabinol [THC]) or nabilone, are available for medical use in several countries (see US, Canada, and UK product information at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm, http://www.medicines.org.uk/emc/, and http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp, respectively; Hazecamp et al., 2013). Some synthetic cannabinoids that fall outside historic regulations in most countries are also included in herbal products marketed for recreational use (Dresen et al., 2010; Fattore & Fratta, 2011).

The pharmacologic effects of most known cannabinoids have not been characterized in detail, although based on available data these effects may differ substantially between very closely related compounds (e.g. THC and cannabidiol [CBD]) (Pertwee, 1997; Pertwee et al., 2010). Potential sites of action of different cannabinoids include...
G-protein coupled receptors (e.g. CB1 or CB2 cannabinoid, opioid, muscarinic, many others), ligand-gated ion channels (e.g. nicotinic, serotonin, glycine), other ion channels (e.g. calcium, potassium, sodium), nuclear receptors (e.g. peroxisome proliferator-activated receptors), and other targets (Pertwee, 1997; Pertwee et al., 2010). Reported clinical effects of cannabinoids and cannabinoid-containing products are accordingly broad, and may include analgesic, antiemetic, anti spasmodic, appetite-stimulating, concentration-diminishing, derealization, dizziness, dysphoric, euphoric, hallucinogenic, muscle relaxant, postural hypotensive, sedative, tachycardic, xerostomic, and numerous other effects (Ashton, 2001; Ben Amar, 2006).

Given the widespread availability and use of cannabinoids in different forms, and their potential to exert clinically significant pharmacologic actions, serious attention is owed to their metabolic fate and effects. The record of these characteristics, however, spans a long history of study that began shortly after the identification of THC as a major psychoactive constituent of cannabis in 1964 (Gaoni & Mechoulam, 1964) The purpose of this review is to summarize the data characterizing the potential for exogenous cannabinoids 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.

Methods

A literature search was conducted of all PubMed (1948–2013) indexes. Articles pairing any included cannabinoid term with any included enzyme and associated drug term (both lists below). English language and human species limits were applied. Titles and abstracts of articles were screened for inclusion. Eligible studies investigated the effects of human drug metabolizing enzymes on exogenous cannabinoids, cannabinoid-containing products and extracts, cannabinoid derivatives, and cannabinoid metabolites, or the effects of these substances on the expression or activity of the enzymes. Data specific to known enzyme isoforms were included in place of more general data when both were available. In vivo and ex vivo human studies were also included when they investigated reactions specific to enzymes of interest, or described pharmacokinetic interactions involving the cytochrome P-450 (CYP-450) related drugs and reactions described below. References cited by included reports were reviewed for additional relevant information, as were prescribing information and summaries of product characteristics for US and UK approved cannabinoid products.

Searches, reference screening, and data extraction were carried out in duplicate, by both authors independently. Eligible studies were assessed using a standard form characterizing study methods, study population (if applicable), compounds and enzymes investigated, and the direction and magnitude of observed effects.

Cannabinoids

The following cannabinoid related search terms were included: tetrahydrocannabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, and tetrahydrocannabinvar (some of the more common phytocannabinoids found on initial review of the topic; Mehmedic et al., 2010) dronabinol and nabilone (U.S. approved synthetic cannabinoids); and the general terms cannabinoid (to capture other cannabinoids not explicitly included), cannabis, hash, hashish, and marijuana.

Enzyme and associated drug terms

The following terms were used for major drug metabolizing enzyme types: enzymes and coenzymes; cytochrome p-450; glucuronosyltransferase; dehydrogenase; sulfotransferase; acetyltransferase; acyltransferase; methyltransferase; transferase; monoxygenase; hydrolase; oxidoreductase; reductace; oxidase; peroxidase; esterase; cholinesterase; and amidase. Additionally, terms for drugs and reactions corresponding to the substrates (preferred, acceptable, sensitive, or not specified), inhibitors (preferred, acceptable, strong, or not specified), and inducers (strong or not specified) of CYP-450 isoforms listed by the U.S. Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers were included, as summarized in Table 1 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, accessed September 20, 2013).

Following the PubMed search and review, two searches of Google Scholar (http://scholar.google.com/) were conducted applying the same inclusion and exclusion criteria. The terms “cannabinoid metabolism” and “human cannabinoid metabolism” were used, and each search was terminated after the first time 100 consecutive results were returned that did not meet inclusion criteria.

Results

A total of 6094 results were generated through the initial PubMed search, which reduced to 2992 after human and English limits were applied. From these, 31 publications meeting inclusion criteria were identified. A further six studies did not meet inclusion criteria but are included in the Results tables and/or Discussion based on their potential relevance to the topic or search terms applied. The Google Scholar search yielded no additional studies meeting inclusion criteria.

In vitro and ex vivo data

Figures 1 and 2 summarize in vitro data describing potential metabolic pathways of cannabinoids, derivatives, and metabolites in vitro. Figure 3 depicts the chemical structure of the parent cannabinoids for which data were found and included. Based on studies to date, (CYP-450) 2C9 and 3A4 are predicted to play major roles in the primary metabolism of THC (Bland et al., 2005; Bornheim et al., 1992; Richardson et al., 1995; Watanabe et al., 1995, 2007). Secondary THC metabolism may occur via several pathways: 7-OH Δ^8-THC by CYP-450 isoforms (primarily 3A4; Matsunaga et al., 2000) 11-OH-Δ^9-THC and 11-nor-9-carboxy-Δ^9-THC (THC-COOH) by several UGT isoforms (Mazur et al., 2009) 11-oxo-Δ^8-THC by CYP-450 isoforms (primarily 2C9; Watanabe et al., 2002) and some epoxide metabolites of Δ^8-THC by epoxide hydrolase (Yamamoto et al., 1984).
Table 1. Search terms for substrates, inhibitors, and inducers of human CYP-450 enzymes *in vitro* and *in vivo*.

| Isoform/Family | Substrate terms                                                                 | Inhibitor terms                                                                 | Inducer terms |
|---------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------|
| 1A2           | Alosetron caffeine etoxyzoresorufin melatonin phenacetin ramelton tacrine theophylline tizanidine | Ciprofloxacin enoxacin fluvoxamine furafylline naphthoflavone | Lansoprazole omeprazole<sup>c</sup> |
| 2A6           | Coumarin nicotine                                                              | Methoxsalen pilocarpine tryptamine                                             | Phenobarbital rifampin |
| 2B6           | Bupropion efavirenz methyphenidin propofol                                        | Adamantane clopidogrel diamantane phenethylamine sertaline ticlopidine           | Rifampin |
| 2C8           | Amodiaquine paclitaxel rosiglitazone repaglinide                                  | Gemfibrozil montelukast pioglitazone quercetin rosiglitazone trimethoprim       | Rifampin |
| 2C9           | Celecoxib diclofenac flurbiprofen phenytoin tolbutamide warfarin                  | Amiodarone fluconazole fluvoxamine fluoxetine sulfaphenazole                    | Rifampin |
| 2C19          | Esomeprazole fluoxetine lansoprazole mephenytoin omeprazole pantoprazole          | Fluconazole fluvoxamine moclobemide nortriptyline omeprazole ticlopidine         | Rifampin |
| 2D6           | Atorvastatin bufuralol debisoxime desipramine dextromethorphan metoprolol nebivolol perphenazine tolterodine venlafaxine | | |
| 2E1           | Aniline chlorothiazide lauric acid nitrophenol                                    | Clomethiazole diallyl disulfide diethylthiocarbamate disulfiram                  | Ethanol |
| 3A<sup>a</sup> | Aldenatil aperitit autoprotid bupropine convaptan darifenacin darunavir dasatinib dextromethorphan dronedaron eletitrapan eplerenone erythromycin everolimus felodipine fluticasone indinavir lopinavir lovastatin lurasidone maraviroc midazolam nifedipine nisoldipine quinapril saquinavir sildenafil simvastatin sirolimus testosterone tironavir tolvaptan triazolam vardenafil | Atazanavir azamulin bocaprevir clarithromycin convaptan grapefruit juice<sup>b</sup> indinavir itaconazole ketoconazole lopinavir mibefradil nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin troleandomycin verapamil voriconazole | Avasimibe carbamazepine phenytoin rifampin St. John’s wort |

Adapted from U.S. Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, accessed September 20, 2013).

Search terms also included for short (e.g. 1A2) and long (e.g. CYP1A2) abbreviated isoenzymes names.

<sup>a</sup>Search included terms for 3A4, 3A5, 3A7, and 3A43.

<sup>b</sup>Shortened to ‘‘grapefruit’’.

<sup>c</sup>Smoking and related terms not included.
Figure 1. Cytochrome P-450 (CYP-450) metabolic pathways for cannabinoids and investigated metabolites based on in vitro data. Supporting data (Bland et al., 2005; Bornheim et al., 1992; Chimalakonda et al., 2012; Jiang et al., 2011; Matsunaga et al., 2000; Richardson et al., 1995; Watanabe et al., 1995, 2002, 2007).

Figure 2. Glucuronidation pathways for exogenous cannabinoids and investigated metabolites in vitro. Supporting data (Chimalakonda et al., 2011; Mazur et al., 2009).

Figure 3. Chemical structures of the parent cannabinoids for which data were found and included in the review. Left side, from top to bottom: THC; CBD; and CBN. Right side, from top to bottom: JWH-018; JWH-073; and AM2201.
THC metabolic findings are generally consistent across overlapping studies, despite variability in the specific form of THC used (Δ8, Δ9, or plant-extracted mixed isomers).

Cannabinol (CBN) is also predicted to undergo significant metabolism via CYPs 2C9 and 3A4 (Watanabe et al., 1995, 2007) and CBD via CYPs 2C19 and 3A4 (Jiang et al., 2011). Both CBN and CBD may also be directly glucuronidated by several UGT isoforms (Mazur et al., 2009). No studies of the secondary metabolism of CBN and CBD were identified.

Two synthetic cannabinoids, JWH-018 and AM2201, are predicted to be metabolized primarily by CYP1A2 and 2C9 (Chimalakonda et al., 2012). JWH-018 and JWH-073, the latter also a synthetic cannabinoids, were not directly glucuronidated by several studied UGT isoforms, while most investigated metabolites were conjugated by multiple isoforms (Chimalakonda et al., 2011).

Table 2 summarizes the available data describing inhibitory potencies of THC, CBD, and CBN at CYP-450 isoforms (Roth et al., 2001; Yamaori et al., 2010, 2011a,b,c, 2012). One additional study identified some potential for CBD to inhibit UGTs 1A9 and 2B7, for CBN to inhibit UGT1A9, and for CBN to possibly activate UGT2B7, all based on the impact of these compounds on ethanol glucuronidation by recombinant isoforms (Al Saabi et al., 2013). No investigations were identified that specifically evaluated potential enzyme activation or induction effects of cannabinoids. One study identified a small dose-dependent activation of phenytoin hydroxylation in human liver microsomes in the presence of THC, 11-OH THC, or THC-COOH (Bland et al., 2005); however, a study in human hepatocytes summarized in the U.K. Summary of Product Characteristics (SPC) for oromucosal cannabis extract (Sativex®, 7/2012) found no relevant induction of CYPs 1A2, 2C9, 2C19, or 3A4 at concentrations of up to 1 μM of a 1:1% v/v THC botanical drug substance and CBD botanical drug substance.

In studies of monoamine oxidase (MAO) function: THC isomers and CBD exerted no or minimal impact on platelet MAO activity ex vivo (the greatest inhibitory effect was exerted by Δ8-THC, with K, 7.8 μM); (Mazor et al., 1982) marijuana had no impact on ex vivo platelet MAO function in the 4 h following smoking (Stillman et al., 1978) and THC and CBD exerted little or no inhibition of liver or brain MAO activity in vitro, although some cannabis extract components may inhibit particularly the MAO-B isoform (Schurr & Rigor, 1984) In long-term cannabis users, cannabis smoking did not affect ex vivo plasma dopamine β-hydroxylase activity acutely, and a 3-day abstinence from cannabis was associated with a <10% increase compared to baseline activity (Markanos & Stefanis, 1982). Finally, a cannabis extract with unknown cannabinoid content had no impact on red blood cell acetylcholinesterase activity in vitro, and a study found similar baseline and 30–60 min post-smoking ex vivo serum acetylcholinesterase activity in regular hashish users compared to tobacco users (Coutselinis & Michalodimitrakis, 1981; Srivastava et al., 2012).

### Clinical data

Published clinical studies meeting inclusion criteria are summarized in Table 3. The pharmacogenetic study by Sachse-Seeboth et al. (2009) found that THC exposure increased and THC-COOH exposure decreased across CYP2C9 genotypes ordered from the expected highest function *1/*1 to the lowest function *3/*3. THC area under the concentrations–time curve (AUC) was approximately 3-fold greater in a small sample of CYP2C9*3/*3 carriers compared to *1/*1 carriers. CYP3A5 variants in this study were associated with no or minimal differences in THC pharmacokinetic variables.

In a clinical study summarized in the U.K. SPC for oromucosal cannabis extract, coadministration of ketoconazole increased the maximum concentration (Cmax) and AUC of THC by 1.2- and 1.8-fold, respectively, those of 11-OH-THC by 3- and 3.6-fold, respectively, and those of CBD each by 2-fold (Sativex®, U.K. SPC 7/2012). The SPC also summarizes a study in which rifampin coadministration decreased the Cmax and AUC of THC by 40% and 20%, respectively, those of 11-OH-THC by 85% and 87%, respectively, and those of CBD by 50% and 60%, respectively. Coadministration with omeprazole, in contrast, caused no significant change in THC, 11-OH-THC, or CBD pharmacokinetic variables.

Oral THC and smoked marijuana did not increase indinavir exposure in a clinical study (Kosel et al., 2002).

Two studies reported a 42–48% higher average estimated theophylline clearance in more frequent marijuana smokers.

### Table 2. Inhibition of human metabolic enzymes by exogenous cannabinoids in vitro.

| CYP-450 isoform | 1A1 | 1A2 | 1B1 | 2A6 | 2B6 | 2C9 | 2D6 | 3A4 | 3A5 | 3A7 |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Δ8-THC         | 4.78 μM<sup>a</sup> | 7.54 μM | 2.47 μM | 28.9 μM<sup>a</sup> | 2.81 μM | 0.94–1.50 μM | 17.1–22.9 μM<sup>a</sup> | >50 μM<sup>a</sup> | 35.6 μM<sup>a</sup> | 30.3 μM<sup>a</sup> |
| CBD            | 0.155 μM<sup>a</sup> | 2.69 μM<sup>a</sup> | 3.63 μM<sup>a</sup> | 55.0 μM<sup>a</sup> | 0.694 μM<sup>a</sup> | 0.95–9.88 μM<sup>a</sup> | 1.16–2.69 μM<sup>a</sup> | 1.00 μM | 0.195 μM | 12.3 μM |
| CBN            | 0.541 μM<sup>a</sup> | 0.0790 μM | 0.148 μM | 39.8 μM<sup>a</sup> | 2.55 μM | 0.88–1.29 μM<sup>a</sup> | 12.3–24.9 μM<sup>a</sup> | >50 μM<sup>a</sup> | >50 μM<sup>a</sup> | 23.8 μM<sup>a</sup> |

Supporting data: (Roth et al., 2001; Yamaori et al., 2010, 2011a,b,c, 2012).

<sup>a</sup>Evidence of enzyme inactivation.

<sup>b</sup>Half maximal inhibitory concentration (IC50). Other reported values are inhibition constants (K<sub>i</sub>.

<sup>c</sup>Evidence of time-dependent inhibition, without further analysis.

Additional analyses in the cited references indicate: Inhibition of CYPs 2B6 (K<sub>i</sub>, 1.29 μM) and 2D6 (IC<sub>50</sub>, 10.2 μM) by cannabidivarin; little or no measurable inhibition of CYP2D6 by mono- and dimethylated CBD derivatives or several polycyclic aromatic hydrocarbons found in marijuana smoke; little or no measurable inhibition of CYP2C9 by several polycyclic aromatic hydrocarbons found in marijuana smoke; and substantially lower inhibition potency of mono- and dimethylated CBD derivatives at CYPs 2A6, 2B6, and 3A compared to CBD.
| Study citation            | N     | Population                                                                 | Relevant groups/treatments                                                                 | Pharmacokinetic results                                                                 | Pharmacokinetic suggestion                                                                 |
|--------------------------|-------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| (Sachse-Seboth et al., 2009) | 43    | Healthy volunteer nonsmokers age 18–65 years genotyped for CYP2C9 *1, *2, and *3, CYP3A5*1 and *3, and SLC01B1 Asn130Asp and Val174Ala alleles. | All subjects given a single dose of 15 mg (-)Δ2-THC (dronabinol) in coconut oil.       | Significant trends of greater THC, lower THC-COOH exposure (AUC, Cmax, C24h) across ordered CYP2C9 types (*1/*1, *1/*2, *2/*2, *1/*3, *2/*3, *3/*3). No similar trend in THC-OH pharmacokinetic variables. Small group of *1/*1 carriers (N=4) had ~3 fold greater median THC AUC, ~70% lower median THC-COOH AUC than *1/*1 carriers (N=19). No or minor association between investigated CYP3A5 and SLC01B1 types and THC or metabolite PK. | Significant increases in THC exposure and decreases in THC-COOH generation possible with low or diminished CYP2C9 function. |
| (Kosel et al., 2002)      | 28    | Patients receiving indinavir (800 mg q8h), with experience smoking marijuana but no cannabinoids within 30 days. | Random assignment to one of the following three times daily, 1 h before meals for 14 days: • Placebo • Marijuana cigarettes (3.95% THC, as tolerated) • (-)Δ2-THC (dronabinol, 2.5 mg orally) | No significant change in indinavir Cmax, AUC, or Cmin between baseline and 14 days, except 14% average decrease in indinavir Cmax in marijuana arm. | Low net CYP3A4 inhibitory/induction potential of marijuana smoking and dronabinol. Parallel study (N=34) finding no significant impact of the same marijuana and dronabinol regimens on nelfinavir Cmax, Cmin, AUC, further supports this conclusion. Possible net induction of theophylline metabolism by marijuana smoking, particularly with use of ≥2 joint/wk. Taken with the Kosel et al. (2002) findings, CYPIA2 is the likely primary pathway affected. |
| (Jusko et al., 1978)      | 57    | Healthy volunteers age 19–47 years, including 7 who reported chronic (≥twice weekly; final cohort average ~4 times/wk) marijuana smoking, 7 who reported chronic marijuana and tobacco smoking, and 24 who reported smoking tobacco only. Average reported tobacco consumption 20–25 cigarettes/day among tobacco smokers. | Subjects all given a single 3–5 mg oral aminophylline dose. | Compared to nonsmokers, marijuana smokers had roughly 42% greater estimated theophylline clearance, similar to tobacco smokers, while combined tobacco and marijuana smokers had roughly 79% greater clearance. | Possible net induction of theophylline metabolism by marijuana smoking, particularly with use of ≥2 joint/wk. Taken with the Kosel et al. (2002) findings, CYPIA2 is the likely primary pathway affected. |
| (Jusko et al., 1979)      | 200   | Patients treated with theophylline (N=100) and historic/literature derived subjects given theophylline (N=100), age <20 to >60, of whom 9 reported marijuana use <1 joint/wk, 14 reported marijuana use ≥2 joint/wk. | Theophylline clearance estimated in all treated patients based on pharmacokinetic data, or derived from previous reports in historic/literature subjects. | Marijuana use ≥2 joint/wk associated with approximate 48% greater average estimated theophylline clearance, compared to an average 4% decline with use <1 joint/wk. | Marijuana use not associated with significant differences in weight-normalized theophylline plasma clearance, controlled for caffeine use, oral contraceptive use, tobacco use, and other variables. |
| (Gardner et al., 1983)    | 49    | Healthy women age 19–30 years, of whom 16 reported marijuana use <1 joint/wk and none reported greater marijuana use. | Subjects all given a single 4 mg/kg oral theophylline dose. | Marijuana use not associated with significant differences in weight-normalized theophylline plasma clearance, controlled for caffeine use, oral contraceptive use, tobacco use, and other variables. | (continued) |
| Study citation          | N  | Population                                                                 | Relevant groups/treatments | Pharmacokinetic results                                                                 | Pharmacokinetic suggestion                                      |
|-------------------------|----|-----------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------|
| (Mwenifumbo et al., 2007) | 190 | Healthy volunteers age 20–59 years, with at least 3 grandparents of black African descent, not receiving known enzyme-inducing medications, of whom 68 reported marijuana use: 1–4 joints/mo ($N = 21$); 5–20 joints/mo ($N = 16$); 24–56 joints/mo ($N = 16$); or 60–200 joints/mo ($N = 15$), 94 subjects reported smoking tobacco. Only subjects with CYP2A6*1/*1 genotype included. | Subjects all given a single nicotine bitartrate dose (4 mg nicotine base) following a 12h period of abstinence from all smoking. | 3'-hydroxycotinine/cotinine concentration ratio 270 min after dosing not significantly different among marijuana use strata when controlled for sex and tobacco smoking status. Estimated nicotine AUC in the 360 min after dosing not significantly different among marijuana use strata when controlled for tobacco smoking status. | Low net CYP2A6 inhibition/induction potential of smoked marijuana. |
| **Studies not meeting inclusion criteria** |    |                                                                             |                             |                                                                                         |                                                                  |
| (Chetty et al., 1994)    | 31  | Inpatients with schizophrenia age 16–45 years initiating chlorpromazine, of whom 5 reported regular cannabis use and 11 reported daily tobacco smoking. | Population PK analysis of therapeutic drug monitoring data using chlorpromazine predose (12h) and 2–4 h post-dose concentrations. | Cannabis use associated with 50% greater average estimated chlorpromazine clearance, controlling for age and tobacco smoking. Estimated increase higher (107%) with combined cannabis and tobacco smoking. | Possible additional support for CYP1A2 induction by marijuana smoking. |
| (Engels et al., 2007)    | 24  | Patients with cancer age 27–67 years receiving either irinotecan or docetaxel. | Two consecutive treatments with irinotecan or docetaxel (60–90 min infusion), first alone then with pretreatment with marijuana containing tea (200 mg in 200 mL; 18% THC, 0.8% CBD; 15 days total, beginning 11 days prior). Premedication for both treatments:  
- Irinotecan: granisetron and dexamethasone 30 min prior, SC atropine  
- Docetaxel: Dexamethasone, for 3 days starting night before. | No significant change in irinotecan, irinotecan metabolite (SN-38 and its glucuronide), or docetaxel pharmacokinetic variables, including AUCs. | Low net inhibitory/induction potential of marijuana tea on major metabolic pathways for these drugs and metabolites, including CYP3A4. |
(≥2 joint/week) compared to non-users (Jusko et al., 1978, 1979). These effects were not seen in lower exposure groups (<1 joint/week; Gardner et al., 1983; Jusko et al., 1979).

Discussion

Metabolic pathways

Several in vitro studies were identified that characterize different effects of human drug metabolizing enzymes on cannabinoids and their metabolites. In particular, significant metabolism via specific CYP-450 isoforms is expected for THC (CYPs 2C9, 3A4), CBD (CYPs 2C19, 3A4) CBN (CYPs 2C9, 3A4), JWH-018 (CYPs 1A2, 2C9), and AM2201 (CYPs 1A2, 2C9) based on these data. CYP-450 enzymes may also contribute to secondary metabolism of THC, and UGTs have been identified as capable of catalyzing both primary (CBD, CBN) and secondary (THC, JWH-018, JWH-073) metabolism of some cannabinoids.

Increases in THC and CBD exposure seen when ketoconazole was coadministered with oromucosal cannabis extract support CYP3A4 as a substantial contributor to metabolism of these compounds (Sativex® U.K. SPC 7/2012). The CYP2C9 dependent metabolism of THC is supported by clinical data indicating a 2–3 fold increase in THC exposure in individuals carrying genetic variants associated with diminished CYP2C9 function (Sachse-Seeboth et al., 2009). The significance of CYP2C19 to the clearance of CBD, in contrast, was not supported by the clinical study with omeprazole (Sativex® U.K. SPC 7/2012). Together, these data suggest a potential for clinically meaningful elevations in THC exposure in individuals with diminished CYP2C9 or 3A4 function, and in CBD exposure in individuals with diminished CYP3A4 function. Further, changes in THC and CBD exposure with rifampin suggest a potential for strong induction of these pathways to cause meaningful reductions in THC and CBD exposure.

Inhibition and induction characteristics

Inhibitory constants and/or half maximal inhibitory concentration values of THC, CBD, and CBN at studied CYP-450 isoforms are generally well below the expected systemic concentrations of these cannabinoids with most use (Marinol® U.S. prescribing information 6/2006; Sativex® U.K. SPC 7/2012; Huestis, 2007; Johannsen et al., 1987; Ohlsson et al., 1982, 1986) Further, regular dronabinol use or marijuana smoking had minimal impact on indinavir pharmacokinetic variables, suggesting a low clinical impact on CYP3A4 function (Kosel et al., 2002). Nonetheless, given the lack of inhibition data at several CYP-450 isoforms, the wide variability in cannabinoid product content and dosing, and the inherent imprecision of using concentration/inhibition potency ratios to predict in vivo drug interaction potential, clinically significant inhibitory effects cannot be ruled out entirely. Notably, the only studies found during this review that suggested clinically evident inhibition of CYP-450s in humans did not meet inclusion criteria, and suggested some possible weak CYP2C inhibition by CBD based on decreases in hexobarbital clearance and 11-hydroxylation of THC with concomitant CBD use (Benowitz et al., 1980; Nadulski et al., 2005).

Although in vitro data suggest a lack of relevant induction of CYPs 1A2, 2C9, 2C19, and 3A4 by plant-extracted THC and CBD, marijuana smoking appears to induce theophylline clearance. CYP1A2 is likely the dominant isoform affected based on relative changes seen in theophylline (a substrate of CYP1A2 and 3A4) and indinavir (primarily a CYP3A4 substrate) exposure (Jusko et al., 1979; Kosel et al., 2002). The connection of this effect to cannabinoids themselves, however, is questionable given the similar effects seen with tobacco smoking, the lack of evidence of induction from studies using non-smoked cannabinoid preparations, and the aforementioned in vitro data (Sativex® U.K. SPC 7/2012).

Data not meeting inclusion criteria

Two studies in Table 3 did not meet inclusion criteria, but are included as they may provide additional insight into the specific pharmacokinetic effects described above (Chetty et al., 1994; Engels et al., 2007). In a population pharmacokinetic analysis, self-reported regular cannabis use was associated with a 50% increase in estimated chlorpromazine clearance (Chetty et al., 1994). This may reflect net CYP1A2 induction by non-THC components of smoked marijuana, consistent with results seen with theophylline. Study data indicating a lack of impact of dronabinol on nelfinavir exposure, or of a marijuana tea on irinotecan or docetaxel exposure, provide additional evidence for a low impact of non-smoked cannabinoid preparations on CYP3A4 mediated metabolism (Engels et al., 2007; Kosel et al., 2002).

Although this review did not aim to comprehensively characterize transport phenomena related to cannabinoids, some potential transporter-related effects were identified. In vitro data were found that suggest: THC inhibition of the ATP binding cassette (ABC) family transporters P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2); (Tournier et al., 2010) CBN inhibition of P-gp, although THC, THC-COOH and CBN were not identified as significant inhibitors in this study; (Zhu et al., 2006) and THC, CBD and CBN inhibition of the BCRP and the ABC transporter multidrug resistance-related protein 1 (MRP1, ABCC1) (Holland et al., 2007, 2008).

Limitations

Some important potential limitations of the methodology of this review should be noted. First, the search strategy, while broad, gives no guarantee that the results are totally comprehensive. The combination of PubMed and Google Scholar was chosen based on some complementary properties, but may not cover all potential data sources (Shultz, 2007). Second, it is likely that some additional support for enzyme-related effects described in this review exist in case reports and studies investigating less common probe drugs or pathways. Two such studies were identified and appended to Table 3, although others may exist. Finally, the exclusion of non-human data may also be viewed as a limitation. However, non-human data were felt to be of at best secondary importance in achieving the primary goal of assessing the potential significance of enzyme related data to human pharmacotherapy.
Conclusion

In conclusion, significant findings relating to the metabolic fate and effects of exogenous cannabinoids have accumulated for over 30 years, yet significant gaps in the data remain. In particular, few in vitro findings have been validated in human studies, except those pertaining to the major metabolic pathways of THC and CBD. The individual who uses cannabinoids, especially those other than THC or CBD, therefore assumes an unclear risk related to metabolic drug interactions. At present, general caution appears warranted particularly when function of the major oxidative cannabinoid metabolic pathways is substantially increased or decreased. Exposure and systemic effects of CYP1A2 substrates may be decreased in individuals who smoke marijuana, although the connection of this effect to the cannabinoids specifically is questionable. Interactions involving cannabinoids are expected to vary considerably in their clinical significance given the wide variability in products, doses, routes of administration, populations using cannabinoids, and other factors.

Declaration of interest

The authors report no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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