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ORIGINAL RESEARCH

The Pharmacokinetics and Pharmacodynamics of a Hemp-Derived "Full-Spectrum" Oral Cannabinoid Product with a 1:1 Ratio of Cannabidiol to Cannabidiolic Acid and Delta-9-Tetrahydrocannabinol to Delta-9-Tetrahydrocannabinolic Acid: A Double-Blind, Placebo-Controlled, Within-Subjects Human Laboratory Study

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Abstract

Aim: To examine the acute pharmacokinetics (PK) and pharmacodynamics (PD) of a patented oral cannabinoid product containing a botanical hemp-derived "full-spectrum" extract with an approximate 1:1 ratio of cannabidiol (CBD) to cannabidiolic acid (CBDA) and delta-9-tetrahydrocannabinol (THC) to delta-9-tetrahydrocannabinolic acid (THCA).

Methods: Healthy adults (n = 15) ingested soft gels containing 0 (placebo), and approximately 1, 2, and 4 mg/kg of total cannabinoids (combination of CBD, CBDA, THC, THCA, and other minor cannabinoids) in an ascending-dose order in four experimental sessions separated by ≥1 week (the placebo condition occurred randomly within the dose sequence). Mean doses (mg) of primary cannabinoids in the active drug conditions were: 1 mg/kg condition (CBD = 41.1, CBDA = 43.7, THC = 2.2, THCA = 1.6), 2 mg/kg condition (CBD = 73.4, CBDA = 77.9, THC = 3.9, THCA = 2.9), and 4 mg/kg condition (CBD = 134.5, CBDA = 142.8, THC = 7.2, THCA = 5.3). PD outcomes (subjective, cognitive, and physiological effects) were measured before and repeatedly for 8 h after dosing. Plasma specimens were collected throughout the 8-h sessions and at 24- and 48-h post-dosing. PK outcomes included peak plasma concentration (C_{max}) and time to maximum concentration (T_{max}).

Results: For PD outcomes, few differences were observed between 1 mg/kg and placebo. However, relative to placebo, 2 mg/kg and 4 mg/kg produced small to moderate increases in subjective drug effects, including abuse liability items (e.g., "like"), and 4 mg/kg also impaired working memory performance. Generally, PD effects peaked 3–5 h post-dosing and returned to baseline by 8 h. Dose-orderly increases in C_{max} were observed for CBD, CBDA, THC, THCA, and their respective metabolites (e.g., 7-COOH-CBD, THCCOOH), which were often detectable 48 h post-dosing. Across all doses, C_{max} for CBDA and THCA was 19–25-fold higher and T_{max} was up to 2-fold earlier compared with CBD and THC, respectively.

Conclusions: Acute administration of a "full-spectrum" hemp-derived cannabinoid product produced dose-orderly effects; the highest dose elicited several adverse events and produced moderate cognitive impairment and subjective intoxication, despite containing a relatively low dose of THC (mean: 7.2 mg). Carboxylated cannabinoids (e.g., CBDA) exhibited substantially greater bioavailability and faster absorption compared with decarboxylated cannabinoids (e.g., CBD). Additional systematic research is needed to characterize how constituent

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profile impacts the effects of cannabinoid products, and more studies directly comparing carboxylated and decarboxylated compounds appear warranted.

Keywords: pharmacokinetics; pharacmodynamics; full spectrum; cannabinoids; CBD; CBDA

Introduction

The 2018 Agriculture Improvement Act (*a.k.a.*, "The Farm Bill") removed hemp, defined as cannabis containing <0.3% of its primary psychoactive constituent, delta-9-tetrahydrocannabinol (THC), and its derivative products from the controlled substances list in the United States.[1] This legislation has led to an expansive retail market of non-THC cannabinoid products, including various products containing cannabidiol (CBD), a non-intoxicating primary constituent of cannabis.[2] Many individuals use retail CBD products for their purported therapeutic benefits for conditions such as anxiety, autism, and posttraumatic stress disorder,[3–5] yet CBD is currently only approved by the U.S. Food and Drug Administration (FDA) for the treatment of rare seizure disorders.[6] Comparable changes in the regulation, availability, and use of hemp/CBD products have occurred in countries beyond the United States as well.

Retail products containing CBD or other cannabinoids are often categorized based on their constituent profile. For example, "isolate" CBD products are those purported to contain only CBD, while "full-spectrum" CBD products are purported to contain CBD plus minor cannabinoids, terpenes, and, oftentimes, low concentrations of THC.[7,8] Importantly, research to characterize the acute effects of so-called "full-spectrum" products is lacking, as prior controlled clinical studies have typically administered CBD or other cannabinoids in isolation, often at doses much higher than those present in retail products.[9] The lack of data on "full-spectrum" products is a critical gap in knowledge because: (1) most available data on the effects of low THC doses consistent with those found in hemp products come from studies that administered THC in isolation, and (2) emerging research suggests that the bioavailability of cannabinoids can be altered when administered together versus alone, suggesting a given amount of THC may be more intoxicating/impairing if administered in combination with other cannabinoids versus in isolation. For example, at least two clinical studies (one administering THC and CBD isolate and the other administering THC- and CBD-dominant whole plant extracts) and one pre-clinical study (administering CBD in isolate and "full-spectrum" forms) have shown that, when THC and CBD are administered together, bioavailability of these cannabinoids is increased compared with when the same doses of THC and/or CBD are administered alone, likely due to competitive metabolism.[8,10,11] While increased bioavailability could result in improved therapeutic efficacy of cannabinoids in some instances, it could also increase the risk for adverse events and reduce the therapeutic window of a cannabinoid product in other instances. Thus, further data on the safety/tolerability of "full-spectrum" hemp products is essential for informing dosing decisions, particularly given that many individuals who use these products are not frequent users of cannabis and have not developed tolerance to the acute effects of THC.

Recently, retail cannabinoid products purported to contain phytocannabinoid acids such as cannabidiolic acid (CBDA) or delta-9-tetrahydrocannabinolic acid (THCA) have emerged. Acidic cannabinoids are naturally occurring in cannabis and are progenitor phytochemicals to the more widely known phenolic phytocannabinoids (e.g., CBD and THC).[12] Phytocannabinoids are generated upon decarboxylation of their acidic cannabinoid counterparts, which can occur *via* heat (as with smoking, vaping, or baking cannabis) or through chemical decomposition over time.[12,13] Historically, oral cannabinoid products have predominantly contained phytocannabinoids which have been fully decarboxylated, meaning acidic cannabinoids such as CBDA/THCA are generally only present in trace amounts or not present at all in most retail hemp/cannabis "edible" products.[14–16]

Though cannabinoid products generally contain mostly decarboxylated phytocannabinoids, CBDA has been shown in pre-clinical studies to retain some medicinal properties of CBD such as anti-inflammatory,[17,18] antioxidant,[19] neuroprotective,[20] immunomodulatory,[21] and antiemetic effects.[22] Moreover, pre-clinical and clinical evidence suggests that the addition of CBDA to an oral formulation may result in greater CBD bioavailability, again likely due

to the competitive metabolism of these two cannabinoids, as evidenced by three-fold increases in plasma concentrations relative to when CBD is administered alone.[23–25] Similarly, while THCA generally does not produce THC-like psychoactive effects, some preclinical *in vitro* and *in vivo* research suggests that THCA may weakly bind to cannabinoid receptors and exhibits some medicinal qualities (e.g., anti-inflammatory, immunomodulatory, neuroprotective, and antineoplastic effects)[12,26]; one theory as to how THCA binds to cannabinoid receptors but lacks psychoactive properties is that, unlike THC, THCA does not cross the blood-brain barrier to reach the central nervous system and thus only activates peripheral (and not central) cannabinoid receptors, though more research is needed to confirm this hypothesis.

Taken together, prior research suggests that there may be benefits to partially retaining acidic cannabinoids in oral cannabinoid formulations. However, more controlled clinical research on products containing acidic cannabinoids and their decarboxylated counterparts is needed, particularly for products containing THC as this compound may produce psychoactive effects and impact abuse liability and safety/tolerability outcomes. The purpose of the present human laboratory study was to examine the pharmacokinetics and pharmacodynamics of a novel hemp-derived oral CBD product in healthy adults which contained a roughly equal proportion of CBD and CBDA, along with low concentrations of THC (<0.3%) and THCA.

Methods

Study design

A double-blind, within-subjects, placebo-controlled, ascending-dose design was utilized for the present study. Participants completed four drug administration sessions, separated by ≥1 week, which consisted of oral ingestion of approximately 1, 2, or 4 mg/kg of total cannabinoids (CBD, CBDA, THC, THCA, and various minor cannabinoids; see below for full drug details), or placebo. The placebo dose occurred at random within the dose sequence. Given the dose escalation design, in instances in which an intermediate dose precipitated an adverse event or untoward drug effect, the study medical monitor determined whether the participant could advance to the next dosing session or if their participation should be discontinued. Each session consisted of a single acute drug exposure, followed by an 8-h data-collection period. During this 8-h period, blood and urine specimens were obtained to characterize the pharmacokinetics of relevant cannabinoids, and pharmacodynamic assessments were completed (see section "Study outcome measures" below). Additionally, in the 2 days after each session, participants returned to the lab to provide more biospecimens (∼24 and ∼48 h after dosing).

The study was conducted at the Johns Hopkins University (JHU) Behavioral Pharmacology Research Unit (BPRU) in the Johns Hopkins Cannabis Science Laboratory. The protocol was approved by the JHU School of Medicine Institutional Review Board (IRB00290381) and conducted under U.S. FDA Investigational New Drug Application (IND) #158,504. The study was preregistered on ClinicalTrials.gov (NCT05049733).

Participant inclusion/exclusion criteria

Primary study inclusion criteria were: (1) aged 18 to 55; (2) in good health as determined by in-person screening (e.g., medical exam, vital signs, routine bloodwork); (3) negative urine drug test for cannabis and other drugs of abuse and negative alcohol breathalyzer at screening and prior to study sessions; (4) self-report experience with cannabis and intentional use of a CBD product within the last 3 years, but no use of cannabis or cannabinoid products in the past 30 days; (5) not be pregnant or nursing (if female) and willing to use an effective form of contraception during study participation (all participants); and (6) weigh between 110 lbs (50 kg) and 220 lbs (100 kg).

Primary study exclusion criteria included: (1) self-report of non-medical use of psychoactive drugs (aside from nicotine, alcohol, or caffeine) in the 30 days prior to study enrollment; (2) history of or current evidence of significant medical condition or psychiatric illness that could put the participant at risk; (3) use of an over the counter (OTC) or prescription medication within 14 days (or 5 half-lives for that specific drug) of experimental sessions that could interfere with study results or participant safety; (4) enrollment in another clinical trial in the past 30 days; (5) self-reported history of adverse reactions to cannabis/CBD products; and (6) history of hypersensitivity to sesame products.

Screening and experimental procedures

Participants were recruited via media advertising (e.g., newspaper, internet) and word-of-mouth communication. Interested participants received an initial screening over the telephone to ascertain possible

eligibility. Individuals who appeared eligible were invited for an in-person screening that consisted of a detailed evaluation of their medical history, a physical examination, and routine blood work (i.e., chemistry, hematology, serology). Additionally, participants completed a urine drug test, an alcohol breathalyzer, and the Timeline Follow-Back to determine drug/alcohol use in the past 90 days.[27] Written informed consent was obtained from all participants at the in-person visit prior to any study procedures.

Participants arrived in the morning for each session and were instructed that they may have one cup of coffee, but no food, before arrival. Upon arrival, participants provided a urine sample to test for pregnancy/recent drug use, completed an alcohol breathalyzer, and self-reported their drug use since their last visit. If the participant tested positive for pregnancy or alcohol/drugs, participants were discharged from the study. Additionally, OTC drugs (including supplements) and prescription medications were recorded and any changes occurring between the screening visit and study sessions were reviewed by the study principal investigator and medical staff to ensure volunteers were still eligible to participate. After intake procedures, participants ate a standard low-fat breakfast of toast and jam, and an intravenous catheter was inserted to facilitate blood sampling throughout the session. After catheter insertion, a baseline blood sample was collected and baseline pharmacodynamic assessments were completed.

After baseline assessments, participants were given a glass of water with the study drug and instructed to orally ingest their assigned dose for that day. Dosing occurred 1 h after consumption of the standardized breakfast. Participants were not allowed to consume anything, including liquids other than water, for 2 h after drug administration. Following drug administration, participants completed pharmacodynamic assessments and provided biospecimens at pre-determined intervals for 8 h (see below). Participants were discharged 8 h after drug administration and were not permitted to drive home (they were required to arrange for transportation, or a car service was provided). For the 2 days after each session, participants returned to the lab for brief follow-up visits to provide additional biospecimens ($\sim$24 and $\sim$48 h after dosing).

Study drug and materials

Active and placebo soft gels were manufactured for the study by Cultivate Biologics, Corp (Louisville, CO, USA). Active soft gels contained sesame oil and a hemp-derived extract with cannabinoids that had been $\sim$50% decarboxylated; these soft gels are a patented drug product (trade name: Ellevet) developed for the treatment of pain, cancer, and epilepsy in mammals.[28] Placebo soft gels were identical in appearance to active soft gels but only contained sesame oil. Each active soft gel contained 37.8 mg of total cannabinoids ($\sim$16.1 mg of CBD, $\sim$17.2 mg of CBDA, $\sim$0.9 mg of THC, $\sim$0.8 mg of THCA, $\sim$1.2 mg of cannabichromene (CBC), $\sim$0.9 mg of cannabichromenic acid (CBCA), $\sim$0.3 mg of cannabigerol (CBG), $\sim$0.4 mg of cannabigerolic acid (CBGA). Dosing was tailored to each participant based on body weight (i.e., approximately 1, 2, or 4 mg/kg of total cannabinoids).

For a given participant, the same number of soft gels was ingested in each session to maintain the study blind. For example, if seven soft gels were needed to reach the highest dose (4 mg/kg) for a participant, that individual ingested seven soft gels in all experimental sessions (for 1 and 2 mg/kg dose conditions, a mix of active and placebo soft gels were ingested). Based on the range of body weights observed in this study, participants received 2–3 active capsules in the 1 mg/kg condition, 4–6 active capsules in the 2 mg/kg condition, and 7–11 active capsules in the 4 mg/kg condition. Mean (SD) doses of CBD, CBDA, THC, and THCA administered in each condition are reported in Table 1. Drug storage and dispensing were handled by the Johns Hopkins BPRU pharmacy.

Study outcome measures

Pharmacodynamic outcomes including subjective drug effects, cognitive performance, and vital signs were assessed at baseline, immediately following drug administration (time "0"), and again at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h after drug administration. Blood samples (7 mL per specimen) were collected via an indwelling

Table 1. Dose of CBD, CBDA, THC, and THCA Administered to Participants in Each Drug Condition

Dose condition	CBD mg/dose (SD)	CBDA mg/dose (SD)	Δ9-THC mg/dose (SD)	Δ9-THCA mg/dose (SD)
1 mg/kg	41.1 (7.7)	43.7 (8.2)	2.2 (0.4)	1.6 (0.3)
2 mg/kg	73.4 (9.5)	77.9 (10.1)	3.9 (0.5)	2.9 (0.4)
4 mg/kg	134.5 (19.9)	142.8 (21.1)	7.2 (1.1)	5.3 (0.8)

Total cannabinoid doses per participant in each condition are given as the mean (SD) mg/dose calculated based on the number of active capsules administered to each participant to achieve the appropriate dose by weight in each condition.

Δ9-THC, Δ9-tetrahydrocannabinol; Δ9-THCA, Δ9-tetrahydrocannabinolic acid; CBD, cannabidiol; CBDA, cannabidiolic acid; SD, standard deviation.

intravenous catheter at the same timepoints, and again at the 24- and 48-h follow-up visits. Once collected, blood specimens were centrifuged at 1200*g* at 4°C for 10 min to separate plasma, which was divided in half and transferred to two plastic cryotubes for storage at −80°C until being shipped on dry ice to the Toxicology Laboratory at the University of Illinois Chicago for quantitative analysis (see below). Urine samples were also collected, but these have yet to be analyzed and will be reported in a subsequent article.

Subjective drug effects. A 21-item cannabis-specific version of the Drug Effect Questionnaire was used to obtain subjective ratings of drug effects.[29] Individual items included ratings of positive/negative effects and behavioral/mood states often associated with cannabis intoxication. Participants rated each item using a 100 mm visual analog scale (VAS) anchored with "not at all" at 0 and "extremely" at 100.

Cognitive/psychomotor performance tasks. Cognitive/psychomotor ability was assessed using four computerized tasks, which are described in detail elsewhere[30]: the divided attention task (DAT), the digit symbol substitution task (DSST), the Paced Auditory Serial Addition Task (PASAT), and the driving under the influence of drugs (DRUID) application (performed on a tablet). The DAT, DSST, and PASAT assessed divided attention, psychomotor ability, and working memory, respectively, while the DRUID calculated a global impairment score based on performance on four brief tasks which measured various aspects of performance (e.g., reaction time, time estimation, balance, divided attention). All participants were trained on each of these tasks to a stable baseline level during the screening session to avoid practice effects during the experiment.

Vital signs. Heart rate (HR, reported in beats per minute, bpm), systolic blood pressure, and diastolic blood pressure were measured in the seated position using an automated monitor.

Pharmacokinetic analysis. Plasma specimens were analyzed for quantitative levels of eight cannabinoids (CBD, CBDA, THC, THCA, CBG, CBGA, CBC, CBN) and six metabolites (7-COOH-CBD, 7-OH-CBD, 6-OH-CBD, 11-OH-THC, THCCOOH, THCCOOH-glucuronide) via gas chromatography-tandem mass spectrometry (GC-MS/MS) and high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS); these methods are described elsewhere.[24,31,32] Samples were only analyzed for 12 of 15 study completers due to limited funds; the first 12 study completers were analyzed (7 males, 5 females), all of whom completed all four experimental conditions. The lower limits of quantification were as follows: 1.0 ng/mL (CBD), 0.5 ng/mL (CBDA), 1.0 ng/mL (THC), 0.5 ng/mL (THCA), 1.0 ng/mL (CBG), 1.0 ng/mL (CBGA), 2.5 ng/mL (CBC), and 1.0 ng/mL (CBN), 2.5 ng/mL (7-COOH-CBD), 5.0 ng/mL (7-OH-CBD), 5.0 ng/mL (6-OH-CBD), 5.0 ng/mL (11-OH-THC), 2.5 ng/mL (THCCOOH), and 2.5 ng/mL (THCCOOH-glucuronide). The upper limits of the assays were 1000 ng/mL, except for THCCOOH and THCCOOH-glucuronide, which each had an upper limit of 500 ng/mL.

Data presentation and analysis. Each pharmacodynamic outcome was analyzed separately using two-way mixed-effects repeated measures analysis of variances with dose condition (4 levels) and time (11 levels) serving as the two within-subject factors. All pharmacodynamic outcomes were analyzed using change-from-baseline data. When a significant main effect of dose or a dose × time interaction was observed, *post hoc* planned comparisons (Dunnett's tests) were used to compare peak change-from-baseline scores of each active dose to placebo (these results are depicted in Supplementary Table S2). Further, for outcomes in which a significant dose × time interaction was observed, additional planned *post hoc* comparison tests were performed to compare mean values for each active dose to placebo at each individual timepoint to characterize differences in the timecourse of pharmacodynamic effects across doses (where applicable, these results are depicted in the individual timecourse graphs in Supplementary Fig. S1). For plasma cannabinoid data, the mean maximum concentration (C_{max}) and mean time to peak concentrations (T_{max}) were determined for each analyte based on descriptive statistics and a non-compartmental pharmacokinetic analysis. For all analyses, statistical significance was defined as an alpha level of <0.05. Analyses were conducted using GraphPad Prism, Version 9 (La Jolla, CA).

Results

Participants

Twenty-five individuals provided informed consent and were screened for eligibility. Of these individuals, 15 (8 males and 7 females) completed the study and were included in data analysis, 9 were deemed

ineligible, and 1 was discharged after completing one session due to poor venous access. Note, one participant (a female who weighed 68.9 kg) included in the final dataset did not progress to the final dosing condition (4 mg/kg) due to experiencing a moderate adverse event at the 2 mg/kg dose (thus, data for the 4 mg/kg dose for that individual was treated as missing in all analyses). Participant demographics and substance use characteristics are in Supplementary Table S1.

In total, there were six adverse events in this study, experienced by four separate participants, all of which were mild or moderate in severity. There were four incidents of dizziness/lightheadedness (two in the 2 mg/kg condition and two in the 4 mg/kg condition), one instance of acute anxiety (2 mg/kg condition), and one occurrence of nausea accompanied with vomiting in the 4 mg/kg condition. These adverse events generally occurred between 2–4 h after drug administration and resolved on their own without medical intervention. As noted above, one individual did not advance to the 4 mg/kg dose due to experiencing an adverse event at the 2 mg/kg dose (specifically, dizziness/lightheadedness accompanied by acute anxiety and tachycardia—peak HR of 130 bpm).

Pharmacodynamic effects

Subjective drug effects. A significant main effect of dose was observed for 14 subjective items including "drug effect," "unpleasant," "pleasant," "like," "high," "sick," "heart racing," "anxious/nervous," "paranoid," "sleepy/tired," "dry mouth," "dry/irritated eyes," "trouble with memory," and "difficulty performing routine tasks" (see Table 2). In general, planned comparisons revealed that peak ratings on these subjective items increased in a dose-dependent manner, with the most frequent significant differences from placebo occurring in the 4 mg/kg condition, followed by the 2 and 1 mg/kg conditions, respectively. Relative to placebo, only 1 item ("drug effect") differed significantly from the 1 mg/kg dose, while 9 items and 12 items differed significantly from the 2 and 4 mg/kg doses, respectively (see Supplementary Fig. S1). Notably, several subjective items indicative of negative effects (e.g., "heart racing," "trouble with memory," "dry mouth") only differed between placebo and 4 mg/kg.

Figure 1 illustrates subjective ratings of "drug effect," "like," "high," and "unpleasant" over time. A significant dose × time interaction was observed for each item displayed in Figure 1 as well as "pleasant," "sick," "dry mouth," "dry/red eyes," "trouble with memory," and "difficulty performing routine tasks." Planned comparisons revealed that the onset of subjective effects was often the fastest, and the duration was the longest, at the highest dose. For example, for "drug effect," ratings significantly increased relative to placebo from 1.5 to 6 h post-dosing for the 4 mg/kg dose, 2 to 5 h post-dosing for the 2 mg/kg dose, and only at a single time point (3 h post-dosing) in the 1 mg/kg dose condition (see Fig. 1).

Cognitive and psychomotor effects. The main effects of dose were observed for each of the four cognitive/psychomotor tasks but planned comparisons on peak change scores did not detect statistically significant differences between any active condition and placebo for the DSST, DRUID, or DAT (see Fig. 2; Table 2). However, on the PASAT, working memory performance was significantly worse in the 4 mg/kg condition relative to the placebo. A significant dose × time interaction was observed for the DRUID, but not the other three tasks. *Post hoc* planned comparisons at individual timepoints found that DRUID scores in the 4 mg/kg condition differed from placebo at the 5-h timepoint only. Though no statistically significant dose × time interaction was observed on the PASAT, DSST, or DAT, qualitative dose-orderly decreases in performance were observed on each of these tasks, with peak reductions in performance generally occurring approximately 3 h post-dosing.

Vital signs. A significant main effect of dose (but no dose × time interaction) was observed for HR (Table 2). Planned comparisons on peak change data revealed that HR increased significantly in the 2 and 4 mg/kg conditions compared with placebo.

Plasma cannabinoid Pharmacokinetics

Primary cannabinoids. Figure 3 displays plasma concentrations over time for CBD, CBDA, THC, and THCA in each dose condition and Table 3 summarizes the C_{max} and T_{max} values for these cannabinoids. Plasma concentrations for each of these four primary cannabinoids was below the limit of quantification at baseline in all experimental sessions. Overall, carboxylated cannabinoids (CBDA and THCA) exhibited greater and more rapid absorption than decarboxylated cannabinoids (CBD and THC), as evidenced by substantially higher C_{max} values and lower T_{max} values. For example, mean C_{max} values for

Table 2. Statistical Analysis Results for Pharmacodynamic Outcomes Using Change-from-Baseline Data

Outcome measures	Drug condition *F*	*p*	Time *F*	*p*	Drug condition × time *F*	*p*
Subjective drug effect						
Drug effect	31.69	<0.0001	12.33	<0.0001	5.88	<0.0001
Unpleasant	9.28	0.0064	5.11	0.0098	2.94	0.0444
Pleasant	8.74	0.0007	5.08	0.0121	2.70	0.0386
Like drug effect	3.21	0.0494	3.64	0.0305	2.65	0.0398
High	36.80	<0.0001	12.15	<0.0001	8.00	<0.0001
Sick	6.78	0.0197	4.37	0.0248	3.71	0.0383
Heart racing	4.78	0.0332	3.07	0.0372	1.94	ns
Anxious/nervous	4.44	0.0291	4.21	0.0168	2.46	ns
Relaxed	1.16	ns	0.86	ns	1.09	ns
Paranoid	4.58	0.0445	3.44	ns	2.93	ns
Sleepy/tired	3.28	0.0455	5.38	0.0038	1.18	ns
Alert	1.00	ns	2.72	ns	0.77	ns
Irritable	0.31	ns	1.31	ns	1.51	ns
Vigorous/motivated	3.77	ns	2.52	ns	1.95	ns
Restless	3.15	ns	3.26	ns	2.07	ns
Munchies	3.06	ns	5.44	0.0093	1.48	ns
Dry mouth	11.01	0.0017	8.08	0.0002	5.58	0.0027
Dry/irritated eyes	9.44	0.005	4.77	0.0093	3.88	0.0131
Trouble with memory	5.74	0.0198	2.92	ns	3.00	0.0319
Throat irritated	2.42	ns	2.74	ns	2.38	ns
Diff. With routine tasks	10.50	0.0021	7.22	0.0042	4.39	0.0063
Cognitive measures						
Digit symbol substitution task (DSST) Total Correct	4.08	0.019	4.24	0.0082	1.56	ns
Paced Auditory Serial Addition Task (PASAT) total correct	9.22	0.0007	3.84	0.014	1.50	ns
Divided attention task (DAT) mean distance from central target	4.39	0.038	5.42	0.0093	1.67	ns
Driving under the influence of drugs (DRUID)	4.11	0.024	2.49	ns	2.51	0.0312
Vital signs						
Heart rate	5.79	0.0075	7.75	0.0003	1.90	ns

ns, not significant ($p > 0.05$).

CBDA were 22–25 times greater than CBD depending on the dose, while mean C_{max} values for THCA were approximately 19 times greater than THC within every dose condition. Across all dosing conditions, the mean T_{max} for CBDA was earlier (1.5–2 h) compared with the T_{max} for CBD (3–4 h). The mean T_{max} for THCA and THC was the same in the 1 and 2 mg/kg conditions (2 h), but in the 4 mg/kg condition, the mean T_{max} for THCA was earlier (2 h) compared with the T_{max} for THC (4 h).

Cannabinoid metabolites and minor cannabinoids. Plasma concentrations of metabolites of CBD and THC are displayed in Figure 4. Mean C_{max} values for cannabinoid metabolites generally increased in a dose-orderly fashion, and mean T_{max} values ranged from 3 to 5 h, depending on metabolite and dose. The primary psychoactive metabolite of THC, 11-OH-THC, was detected following administration of the 2 and 4 mg/kg doses in select participants (2 mg/kg: 6/12 participants; 4 mg/kg: 11/12 participants) and the CBD metabolite 6-OH-CBD was never detected. Notably, 11-OH-THC and 6-OH-CBD had a higher limit of quantitation (5 ng/mL) than the other analytes, which likely explains why they were detected less often. The CBD metabolites 7-COOH-CBD and 7-OH-CBD and the THC metabolites THCOOH and THCCOOH-glucuronide were often detected 48 h post-dosing (the final blood collection timepoint). Six out of 12 participants had elevated levels of 7-COOH-CBD at baseline in at least one experimental session; these elevated baseline levels always occurred in sessions 2, 3, or 4 and the preceding session was always an active dose (this fact, combined with the lack of detection of parent cannabinoids such as CBD or THC, suggests these elevated metabolite concentrations were likely due to the study dose from the prior week as opposed to cannabinoid use outside of the study). Finally, two minor cannabinoids, CBGA and CBC, were detected (see Fig. 5) while two others (CBG and CBN) were not.

Discussion

There is growing interest in the use of CBD and other cannabinoids for therapeutic purposes, but more controlled clinical studies are needed to understand factors that impact the acute effects and pharmacokinetics of these drugs to inform dosing decisions. To date, most controlled clinical studies have administered CBD or

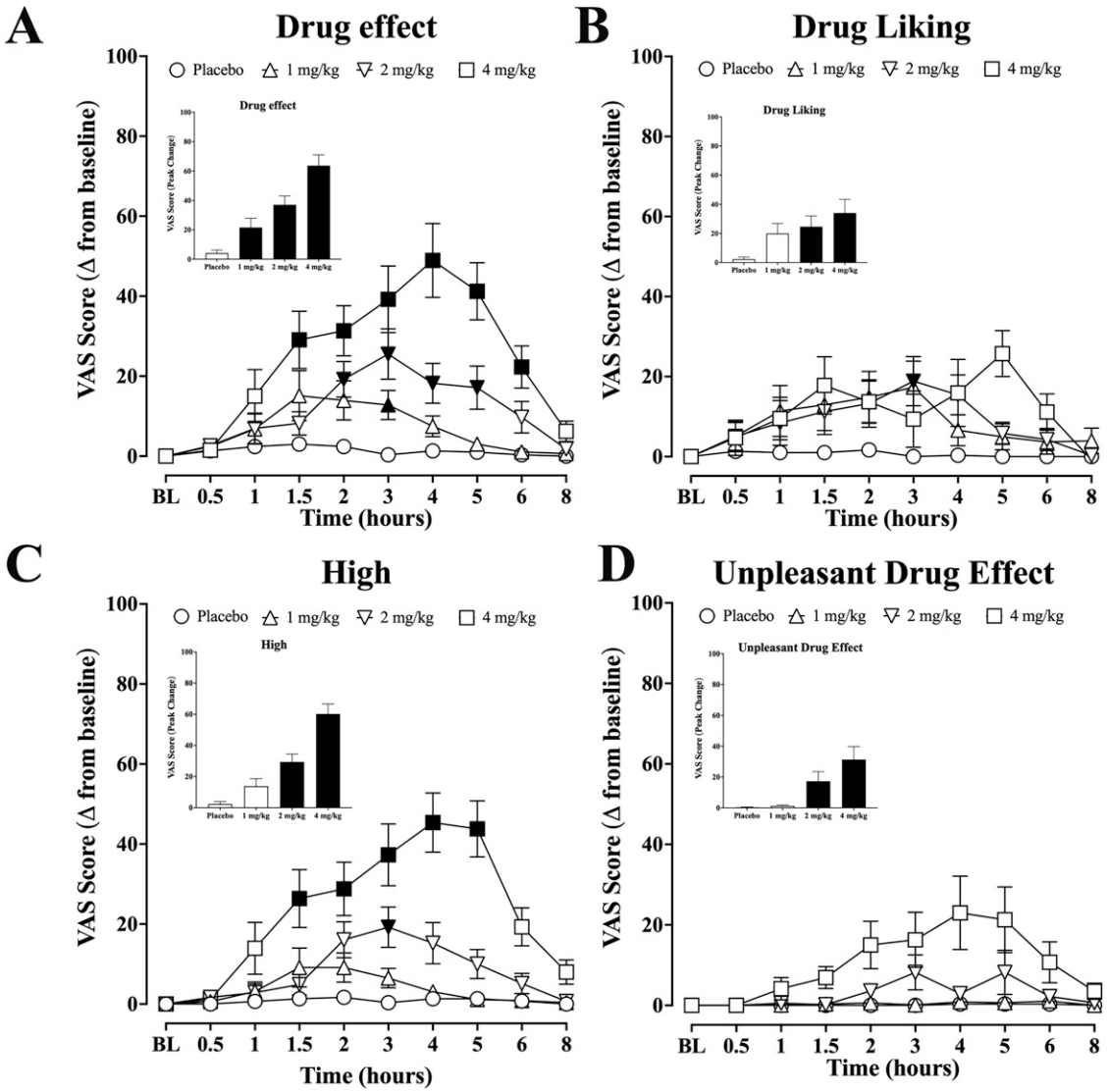

FIG. 1. Change-from-baseline mean ratings for visual analog scale items: **(A)** drug effect, **(B)** drug liking, **(C)** high, **(D)** unpleasant drug effect from the drug effect questionnaire displayed over time. VAS scores ranged from 0 (not at all) to 100 (extremely). Smaller graphs depict the peak change in VAS score responses for each respective outcome (peak change values for individual participants could have occurred at any time point). Error bars correspond to the standard error of the means at individual time points. Black symbols represent a significant difference from the placebo condition at that individual time point, and black bars also represent a significant difference from the placebo condition for peak change data ($p < 0.05$). The sample size for pharmacodynamic outcomes was $n = 15$. VAS, visual analog scale.

other cannabinoids of interest in isolation, yet "full-spectrum" products containing CBD plus various other cannabis constituents (including low concentrations of the psychoactive cannabinoid THC) are widely available. Further, there is a dearth of clinical data on carboxylated cannabinoids (e.g., CBDA); these naturally occurring precursor phytochemicals to cannabinoids (e.g., CBD) are increasingly being retained in retail oral cannabinoid products, which is a relatively new practice. The present human laboratory study sought to fill these knowledge gaps by characterizing the acute pharmacodynamic and pharmacokinetic effects of a novel hemp-

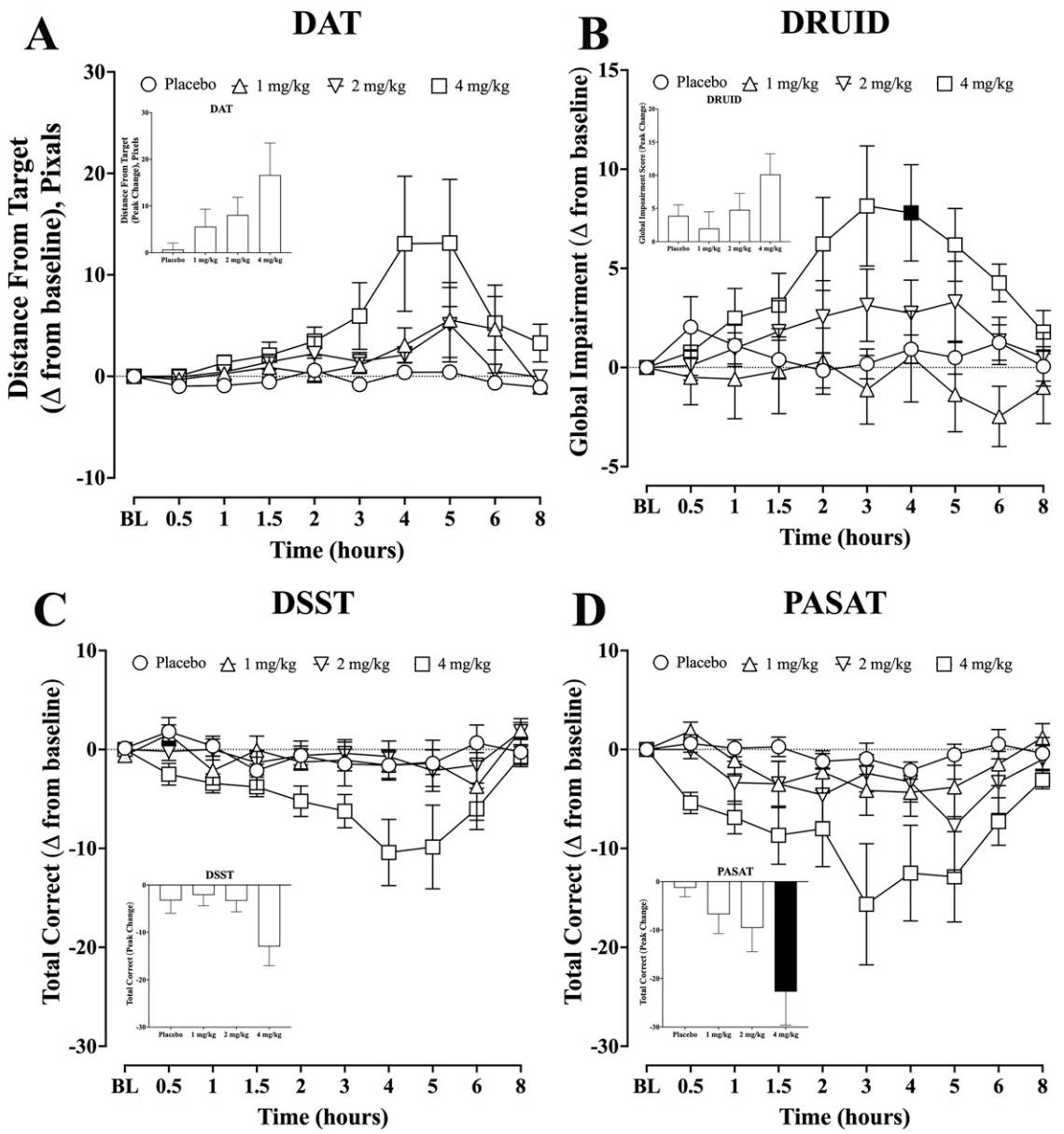

FIG. 2. Change from baseline in average distance from the central stimulus from the **(A)** divided attention task (DAT), in global impairment score on the **(B)** DRUID application, and from baseline mean total correct on **(C)** digit symbol substitution task (DSST), and **(D)** Paced Auditory Serial Addition Task (PASAT) displayed over time. Higher scores indicate worse performance relative to baseline for measures shown in panels A and B. Lower scores indicate worse performance relative to baseline for measures shown in panels C and D. Smaller graphs depict the peak change in cognitive/psychomotor performance for each respective outcome (peak change values for individual participants could have occurred at any time point). Error bars correspond to the standard error of the mean in each drug condition. Black symbols represent a significant difference from the placebo condition at that individual time point, and black bars also represent a significant difference from the placebo condition for peak change data ($p < 0.05$). The sample size for pharmacodynamic outcomes was $n = 15$. DRUID, driving under the influence of drugs.

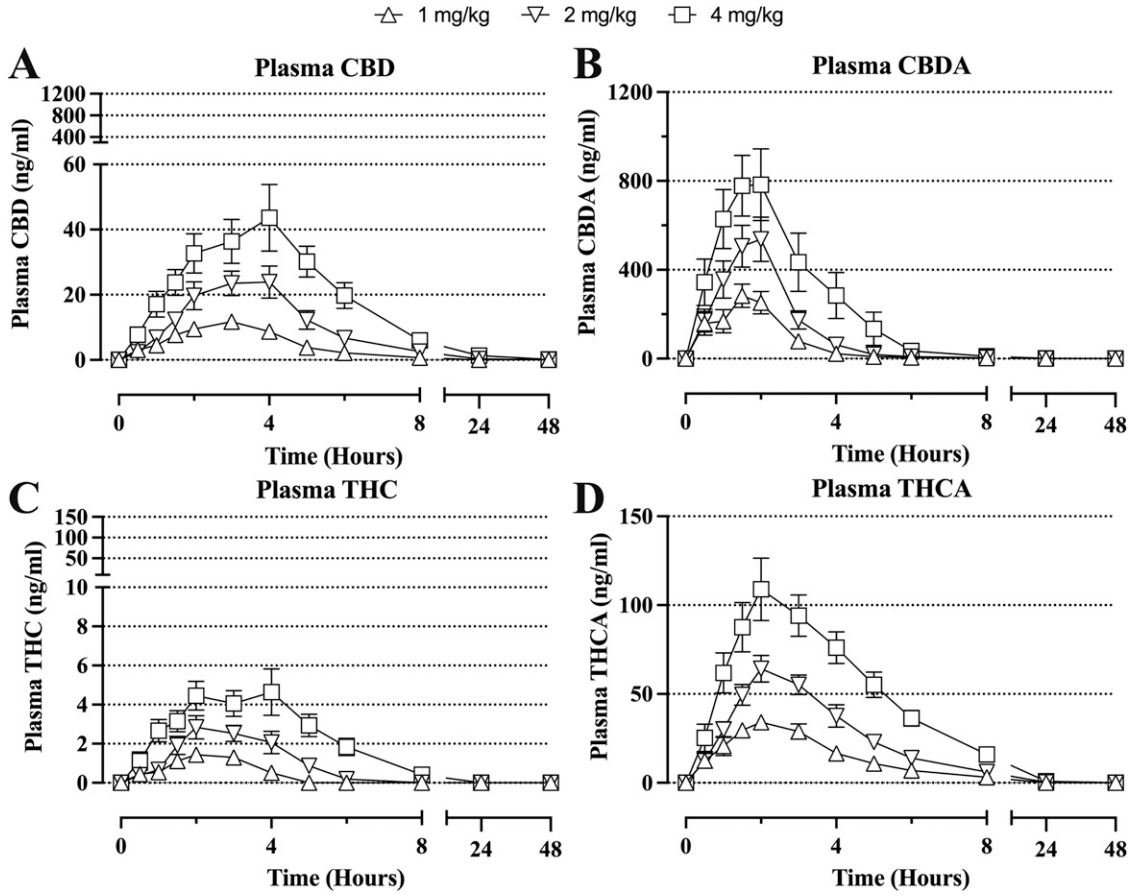

FIG. 3. Mean plasma concentrations for **(A)** CBD, **(B)** CBDA, **(C)** Δ9-THC, and **(D)** Δ9-THCA over time. Error bars indicate the standard error of the means for each drug condition at individual time points. The limits of quantification were 1.0 ng/mL for CBD and THC and 0.5 ng/mL for CBDA and THCA. The sample size for all pharmacokinetic outcomes was (n = 12). CBD, cannabidiol; CBDA, cannabidiolic acid; Δ9-THC, Δ9-tetrahydrocannabinol; Δ9-THCA, Δ9-tetrahydrocannabinolic acid.

derived "full-spectrum" oral CBD product which contained a roughly equal proportion of CBD to CBDA, along with low concentrations of THC, THCA, and other minor cannabinoids.

Overall, the study drug exhibited dose-orderly pharmacodynamic effects. The lowest dose of 1 mg/kg of cannabinoids (mean doses: CBD = 41.1 mg, CBDA = 43.7 mg, THC = 2.2 mg, THCA = 1.6 mg) produced very mild subjective effects with no signal of abuse liability or cognitive impairment, while 2 mg/kg (mean doses: CBD = 73.4 mg, CBDA = 77.9 mg, THC = 3.9 mg, THCA = 2.9 mg) produced more moderate subjective effects (including positive effects indicative of abuse liability such as drug "liking") but no impairment, and 4 mg/kg (mean doses: CBD = 134.5 mg, CBDA = 142.8 mg, THC = 7.2 mg, THCA = 5.3 mg) produced the strongest subjective drug effects (including positive and negative effects) as well as significant impairment of cognitive functioning. These pharmacodynamic effects were likely driven by THC given the other cannabinoids in the study drug are not considered intoxicating. Of note, the study drug contained <0.3% THC and was thus a federally legal hemp product;[1,2] there are many analogous "full-spectrum" CBD products on the market with comparable levels of THC which oftentimes do not specify the presence of THC on their label.[2,15,16,33] Relevant stakeholders (e.g., cannabinoid consumers, regulators, physicians, retail/dispensary employees) should be aware that "full-spectrum" cannabinoid products containing low levels of THC can

Table 3. Average C_{max} and T_{max} for Carboxylated and Decarboxylated Primary Cannabinoids (CBD, CBDA, THC, and THCA) Across Dose Conditions

	CBD		CBDA		THC		THCA	
Dose condition	C_{max} ng/mL (SD)	T_{max} hr (range)	C_{max} ng/mL (SD)	T_{max} hr (range)	C_{max} ng/mL (SD)	T_{max} hr (range)	C_{max} ng/mL (SD)	T_{max} hr (range)
1 mg/kg	15.4 (7.9)	3 (1–4)	385.6 (165.7)	1.5 (0.5–2)	2.2 (1.0)	2 (0.5–4)	42.6 (16.1)	2 (0.5–3)
2 mg/kg	32.3 (18.7)	4 (1.5–4)	713.9 (313.4)	2 (0.5–3)	4.0 (2.3)	2 (1.5–4)	75.4 (19.4)	2 (1–4)
4 mg/kg	56.0 (34.9)	4 (1.5–6)	1231 (471.3)	2 (0.5–5)	6.6 (3.8)	4 (1–5)	126.6 (50.9)	2 (1–4)

Plasma concentrations reported as the mean (SD) of observed C_{max} values among individual participants. T_{max} values reported as the time to reach the mean maximum plasma concentration in hours and the range of timepoints at which C_{max} was observed for individual participants. The sample size for pharmacokinetic parameters was $n = 12$.

CBD, cannabidiol; CBDA, cannabidiolic acid; C_{max}, maximum plasma concentration; hr, hour; SD, standard deviation; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; T_{max}, time to maximum concentration.

elicit impairment and adverse effects for some individuals, thereby limiting the therapeutic window of these drugs and possibly presenting safety concerns in certain situations (e.g., while driving).

Notably, the magnitude of pharmacodynamic effects in the present study was generally greater than those observed in prior studies that orally administered high-THC cannabis or pure THC (e.g., dronabinol) at similar doses.[30,34,35] For example, in one study, ingestion of 7.5 mg of dronabinol did not significantly alter ratings of "drug effect" or impact cognitive performance on the DSST relative to placebo among infrequent cannabis users (same population as the present study).[34] In a similar vein, in prior studies in our laboratory,[30,35] brownies containing high-THC cannabis of slightly higher doses (i.e., 10 mg THC) have produced only mild subjective drug effects and no signs of cognitive/psychomotor impairment among infrequent cannabis users. For instance, in one study,[35] a cannabis brownie containing 10 mg THC produced mean peak ratings of "drug effect" of 18 (out of 100), while peak ratings of "drug effect" in the current study at the 4 mg/kg dose (which contained 7.2 mg THC, on average) was 49 (out of 100).

The stronger pharmacodynamic effects observed in the present study relative to prior studies that included comparable doses of pure THC (or high-THC cannabis) may be attributed to pharmacokinetic interactions between THC and other cannabinoids (e.g., CBD) in the study drug. Prior studies have shown that CBD inhibits the metabolism of THC when these cannabinoids are orally ingested together, which, in turn, facilitates greater pharmacodynamic effects compared with when THC is administered alone.[10,11] It is also possible that CBDA, THCA, and other cannabinoids in the study drug beyond CBD may have further altered the metabolism of THC, though no studies have examined if there are pharmacokinetic interactions between these cannabis constituents. Importantly, because the present study did not include a CBD- or THC-only condition, we were unable to determine the extent to which competitive cannabinoid metabolism accounted for the observed pharmacodynamic effects. Moreover, we were largely unable to compare our results to the studies mentioned above that orally administered similar doses of pure THC or THC-dominant cannabis because those studies either did not report pharmacokinetic data or collected whole blood samples instead of plasma (these two blood matrices yield very different quantitative drug concentrations). Future studies should include both "full-spectrum" and cannabinoid-only comparison conditions to systematically explore the interactive effects of various cannabinoids on drug metabolism.

Another key finding of the present study was that, in general, the magnitude and speed of absorption were substantially greater for acidic cannabinoids (e.g., CBDA) compared with their non-acidic (i.e., decarboxylated) counterparts (e.g., CBD). For example, the C_{max} for CBDA was 22–25-fold greater than that of CBD, and the T_{max} for CBDA was roughly half that of CBD (indicative of faster absorption). This finding is consistent with several prior pre-clinical studies[24,25,36] and at least one clinical study,[37] which simultaneously administered CBD and CBDA, though the magnitude of difference between acidic and non-acidic cannabinoids was markedly greater in the present study. The greater absorption of CBDA (and other acidic cannabinoids such as THCA) is noteworthy because these compounds have been shown to retain some potential therapeutic properties of their decarboxylated counterparts, albeit only in pre-clinical

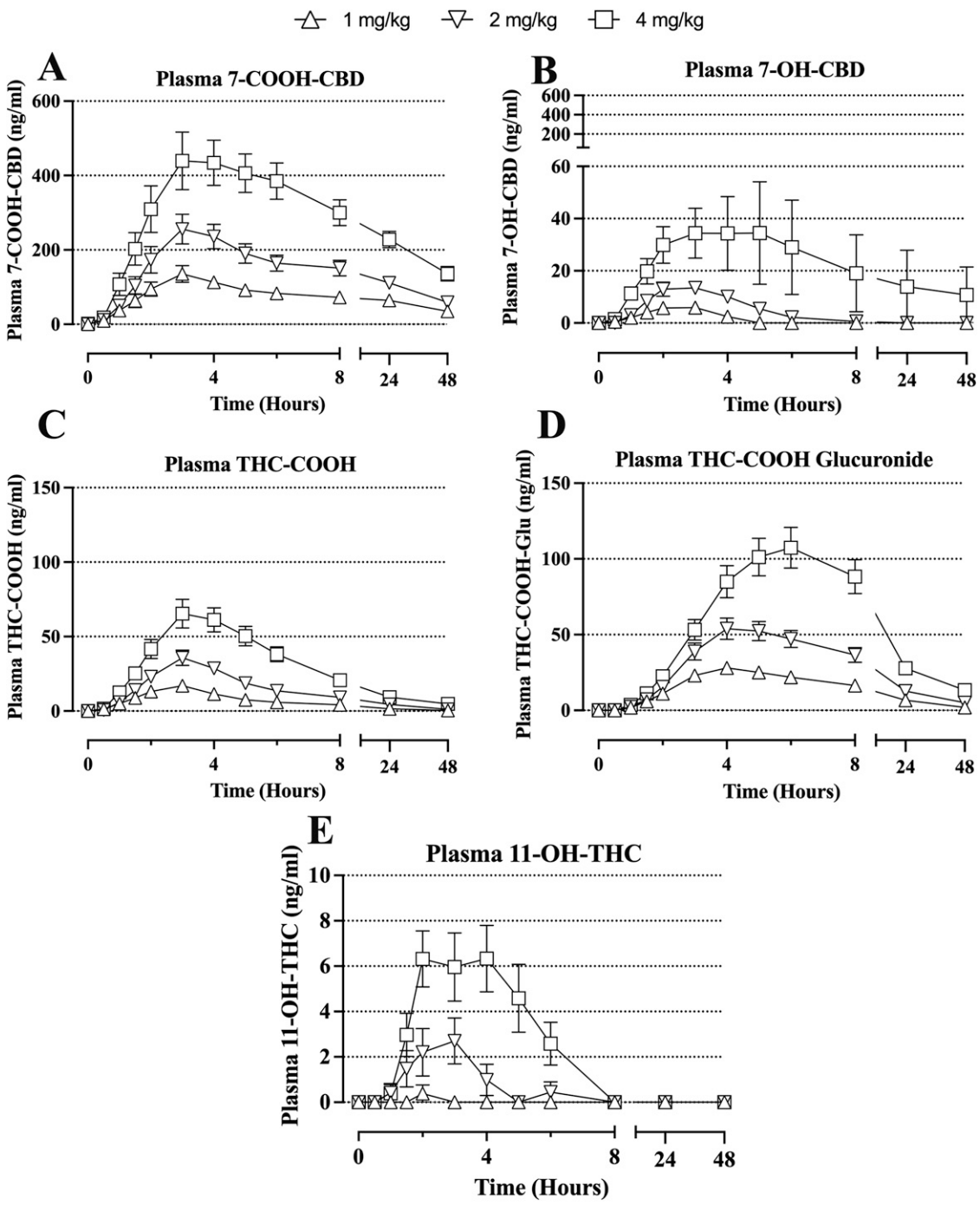

FIG. 4. Mean plasma concentrations for **(A)** 7-COOH-CBD, **(B)** 7-OH-CBD, **(C)** THCCOOH, **(D)** THCCOOH-glucuronide, and **(E)** 11-OH-THC displayed over time. Error bars indicate the standard error of the means for each drug condition at individual time points. The metabolite 6-OH-CBD was never detected. The limits of quantification were 2.5 ng/mL for 7-COOH-CBD, THCCOOH, and THCCOOH-glucuronide, and 5.0 ng/mL for 7-OH-CBD, 6-OH-CBD, and 11-OH-THC. The sample size for all pharmacokinetic outcomes was $n = 12$. CBD, cannabidiol; THC, tetrahydrocannabinol.

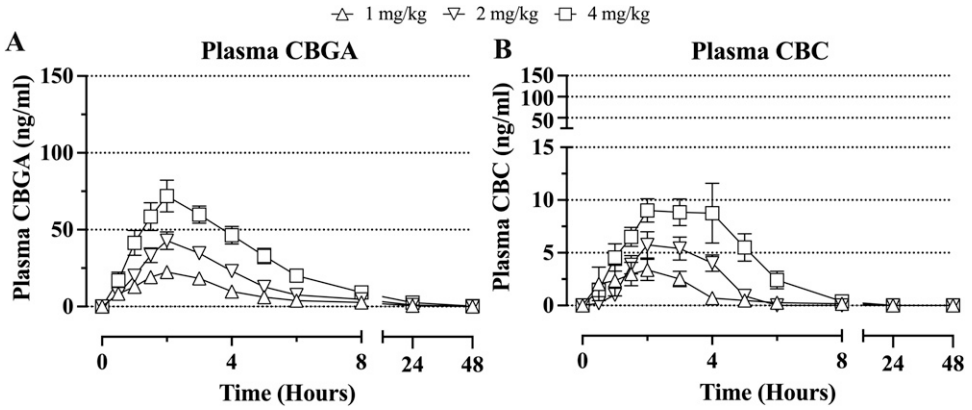

FIG. 5. Mean plasma concentrations for **(A)** CBGA and **(B)** CBC over time. Error bars indicate the standard error of the means for each drug condition at individual time points. CBN and CBG were never detected. The limits of quantification were 1.0 ng/mL for CBG, CBGA, and CBN and 2.5 ng/mL for CBC. The sample size for all pharmacokinetic outcomes was $n = 12$.

studies.[12,17–22] Moreover, acidic cannabinoids are also believed to lack certain properties (e.g., psychoactive effects, abuse liability) known to sometimes limit the therapeutic potential of decarboxylated cannabinoids.[12,26] Thus, a logical future area of clinical research is to examine whether oral formulations with both acidic and non-acidic cannabinoids such as the one examined here result in better therapeutic outcomes compared with isolated cannabinoids, which may occur through direct effects of the acidic cannabinoids themselves and/or enhancement of the bioavailability of decarboxylated cannabinoids with known therapeutic benefits (e.g., CBD) as has been shown previously.[23]

The present study had several limitations. First, as mentioned above, there was not a CBD- or THC-only comparator condition, which hindered pharmacodynamic and pharmacokinetic data interpretation in some respects. Second, participants were only exposed to a single acute dose of the study drug in a given week, which may not be representative of an individual using this product for medicinal purposes; it is possible that safety/tolerability may have improved with repeated dosing (particularly of the 2 and 4 mg/kg doses) as has been shown with other cannabinoid formulations containing comparable levels of THC.[38] Finally, the study was underpowered to examine sex differences or the influence of other participant-level factors on pharmacodynamic and pharmacokinetic outcomes, which is of increasing importance.

In summary, the present study demonstrated that a novel hemp-derived "full-spectrum" oral cannabinoid product (containing <0.3% THC) that was partially decarboxylated elicited dose-orderly increases in pharmacodynamic outcomes. Moreover, a drastically different pharmacokinetic profile was observed for acidic versus decarboxylated cannabinoids, such that the speed and magnitude of absorption were markedly greater for CBDA/THCA compared with CBD/THC. Lastly, the degree of cognitive impairment and subjective intoxication was higher than expected given the relatively low doses of THC in the study product (mean THC dose in the high dose condition = 7.2 mg), possibly due to enhanced absorption of THC via competitive metabolism with the other constituents in the product. These results have important clinical and regulatory implications considering retail hemp-derived "full-spectrum" products used for therapeutic purposes often contain low levels of THC commensurate with those administered here and underscore the importance of complete and accurate cannabinoid content labeling on all retail cannabis/hemp products; moreover, additional information/disclaimers on product labels may be useful for increasing consumer education regarding the expected effects of various cannabinoid product formulations. These data also highlight that additional research examining the pharmacokinetics, safety/tolerability, and therapeutic utility of different cannabinoid formulations (e.g., isolated versus "full-spectrum" products) is warranted.

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Authors' Contributions

T.R.S., H.J.E., and C.A.Z. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: T.R.S., R.V., B.D., J.W., and C.K. Acquisition, analysis, or interpretation of data: T.R.S., H.J.E., and C.A.Z. Drafting of the article: T.R.S., H.J.E., and C.A.Z. Critical revision of the article for important intellectual content: All authors. Statistical analysis: H.J.E. and C.A.Z. Obtained funding: T.R.S. Administrative, technical, or material support: all authors. Study supervision: T.R.S. and R.V.

Author Disclosures Statement

T.R.S. has served as a consultant for Canopy Health Innovations, Inc. and is receiving research funding from Cultivate Biologics (for this project). R.V. has received personal fees from Canopy Health Innovations, MyMD Pharmaceuticals, Mira1a Therapeutics Inc., Syqe Medical Ltd., Radicle Science Inc., Jazz Pharmaceuticals, Charlotte's Web, and WebMD outside the submitted work. E.M.W. has received funding from MyMD Pharmaceuticals and Mira1a Therapeutics Inc. for preclinical cannabinoid research. Co-authors B.D., J.W., C.K., and R.D. are employed by Cultivate Biologics, Corp. The remaining authors have no disclosures to report.

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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Abbreviations Used

CBC = cannabichromene
CBCA = cannabichromenic acid
CBD = cannabidiol
CBDA = cannabidiolic acid
CBG = cannabigerol
CBGA = cannabigerolic acid
C_{max} = peak plasma concentration
FDA = Food and Drug Administration
OTC = over the counter
PD = pharmacodynamics
PK = pharmacokinetics
THC = delta-9-tetrahydrocannabinol
THCA = delta-9-tetrahydrocannabinolic acid
T_{max} = time to maximum concentration
VAS = visual analog scale