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Pharmacokinetic Variability of Oral Cannabidiol and Its Major Metabolites after Short-Term High-Dose Exposure in Healthy Subjects

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Keywords
Cannabidiol · 7-Hydroxy-cannabidiol · 7-Carboxy-cannabidiol · Pharmacokinetic variability

Abstract

Introduction: Cannabidiol (CBD) is a widely utilized non-psychoactive cannabinoid available as a prescriptive drug treatment and over-the-counter supplement. In humans, CBD is metabolized and forms the major active metabolite 7-hydroxy-cannabidiol (7-OH-CBD), which is further metabolized to 7-carboxy-cannabidiol (7-COOH-CBD). In the current study, plasma concentrations of CBD, 7-OH-CBD, and 7-COOH-CBD were measured, and the potential influences of sex, race, and body mass index (BMI) on the pharmacokinetic variability were assessed. ***Methods:*** Blood samples from a previously conducted CBD drug interaction study in healthy volunteers (n = 12) were utilized. The subjects received orally administered CBD (Epidiolex®), 750 mg twice daily for 3 days and a single dose on the 4th day. Nine plasma samples were collected, and plasma concentrations of CBD, 7-OH-CBD, and 7-COOH-CBD were analyzed by LC-MS/MS. Peak plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC), and metabolite-to-parent drug exposure ratios (MPR) were calculated. Statistical analysis was performed to determine the correlations of C_{max}, AUC, and MPR of CBD, 7-OH-CBD, and 7-COOH-CBD in different sex, race, BMI, and body weight. ***Results:*** For CBD, the mean C_{max} was 389.17 ± 153.23 ng/mL, and the mean AUC was 1,542.19 ± 488.04 ng/mL*h. For 7-OH-CBD, the mean C_{max} was 81.35 ± 36.64 ng/mL, the mean AUC was 364.70 ± 105.59 ng/mL*h, and the mean MPR was 0.25 ± 0.07. For 7-COOH-CBD, the mean C_{max} was 1,717.33 ± 769.22 ng/mL, the mean AUC was 9,888.42 ± 3,961.47 ng/mL*h, and the mean MPR was 7.11 ± 3.48. For 7-COOH-CBD, a 2.25-fold higher C_{max} was observed in female subjects (p = 0.0155) and a 1.97-fold higher AUC for female subjects (p = 0.0285) with the normalization of body weight. A significant linearity (p = 0.0135) of 7-OH-CBD AUC with body weight in females was observed. No significant differences were identified in C_{max}, AUC, and PMR with race and BMI. ***Conclusion:*** Observed differences in sex were in agreement with previously reported findings. A larger population pharmacokinetics study is warranted to validate the observed higher C_{max} and AUC in females and significant linearity with body weight in females from the current study.

Introduction

Cannabidiol (CBD) is a nonpsychoactive cannabinoid that is widely used as an over-the-counter supplement, a component of medical cannabis, and a US FDA-approved treatment for specific childhood epilepsies (Epidiolex®). In 2021, CBD was the top-selling herbal supplement ingredient in natural retail stores [1]. The FDA has maintained

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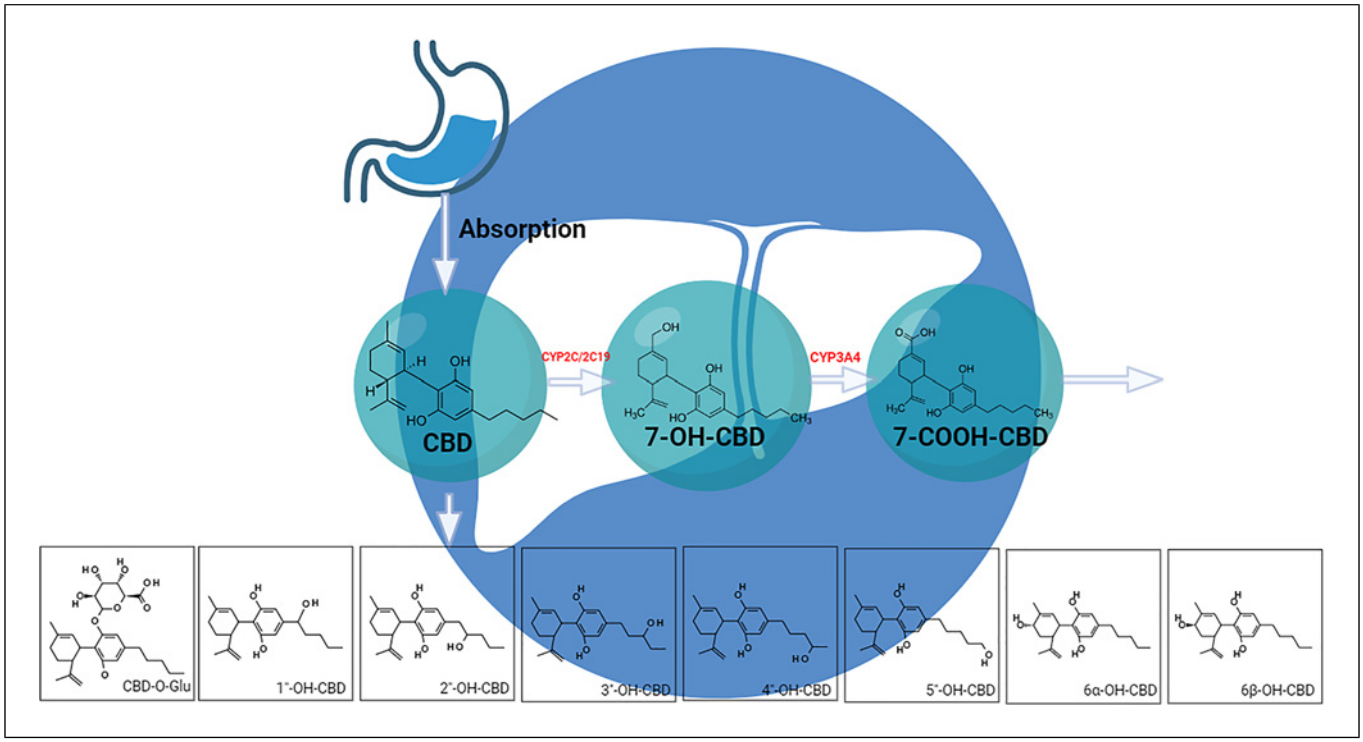

Fig. 1. Primary metabolic pathway for CBD in humans.

that CBD is an unapproved drug when sold as a dietary supplement or in products for external use [1]. In June 2018, the FDA-approved Epidiolex®, the first pharmaceutical drug to contain a purified form of CBD derived from the cannabis plant. Its labeled indications are the treatment of seizures associated with the Lennox-Gastaut syndrome and the Dravet syndrome [2]. The primary clinical outcome of treatment is a significant (38.9–41.9%) median reduction in the frequency of seizures in patients with the two syndromes who were only given CBD [3–5].

However, the pharmacology, toxicology, and pharmacokinetics (PK) of CBD in human subjects are not fully understood. In vitro, CBD acts as a negative allosteric modulator of CB1 receptors [6]. CBD also exhibits anti-inflammatory effects and regulatory effects on the immune system in the periphery [7]. In humans, CBD is readily metabolized to the major active metabolite 7-hydroxy-cannabidiol (7-OH-CBD) by both cytochrome P450 (CYP) 2C19 and 2C9 [8, 9]. The 7-OH-CBD metabolite is reported to possess similar pharmacological activity to the parent compound [9], and it is further metabolized to 7-carboxy-cannabidiol (7-COOH-CBD) by CYP3A4 [10], which is a major inactive metabolite that attains concentrations exceeding those of the parent compound (shown in Fig. 1) [11].

Orally administered CBD is highly metabolized, and it is known to exhibit high interindividual PK variability [12]. The half-life of orally administered CBD in humans has been reported to range from 14.43 to 60.54 h at varying dosages [13]. In one recent exploration of population PK parameters, up to 60% of variability was observed which could not be explained by any patient demographic covariates (age, sex, race) [12]. Furthermore, relatively few PK studies have included the major CBD metabolites in their variability analysis. Due to the incomplete understanding of CBD and its metabolites' pharmacology and toxicology, it is unknown if the high variability may result in differences in CBD's effectiveness and tolerability among different subjects and populations. With regard to the treatment of seizures with FDA-approved CBD, current recommendations are to base dosage on subject weight. In the treatment of epilepsy, dosing strategies for most antiepileptic drugs are guided by therapeutic drug monitoring of blood levels, which can permit greater individualization of drug therapy [14]. This is not presently possible with CBD.

A previously conducted drug interaction study involving the short-term, high-dose administration of a standardized oral CBD solution to 12 healthy volunteers

permitted the repurposing of collected samples for the assessment of CBD and major metabolite PK. The complete details of that study are published elsewhere [15]. In one study arm, the subjects received 750 mg of oral CBD twice daily for 3 days and an additional 750 mg dose on the morning of the 4th day which also served as the serial blood sampling day for the study. In the present report, the potential influences of sex, race, and body mass index (BMI) on the PK variability of CBD, 7-OH-CBD, and 7-COOH-CBD were assessed.

Materials and Methods

Study Design

In brief, a randomized cross-over clinical study was conducted in which non-medicated, nonsmoking healthy volunteers with normal renal and hepatic function (n = 12; 6 males, 6 females, aged 21–44 years old) received oral CBD solution (Epidiolex®). They received 750 mg twice daily for 3 days, followed by a single 750 mg dose the morning of the 4th day [15]. Prior to dosing, subjects were fed a standardized breakfast (bagel, cream cheese, and orange juice) consumed over approximately 30 min. A total of nine blood samples were collected including immediately before the 4th day dose and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h afterward. Collected samples were placed on ice until processing. Separated plasma was stored at −70°C until analysis. As part of the drug interaction assessment, 10 mg of methylphenidate (MPH) was administered to subjects on the day of sample collections. The study protocol and informed consent document, inclusive of Health Insurance Portability and Accountability Act language, were approved by the University of Florida Investigational Review Board (NCT04603391). All of the subjects provided written informed consent.

Bioanalytical Method

The LC-MS/MS bioanalytical method for CBD was previously described [15]. The bioanalytical method for 7-OH-CBD and 7-COOH-CBD was based on a previously reported method with modifications [16]. In brief, 0.5 mL of plasma was mixed with 0.5 mL water, which contained 100 ng/mL d_3-CBD as the internal standard. The mixture was then extracted with 2 mL butyl chloride/acetonitrile (4:1, vol:vol). The organic phase was transferred to clean glass tubes, and it was evaporated to dryness under a gentle stream of nitrogen. The residue was redissolved in the initial mobile phase (80:20 methanol:water) for the LC-MS/MS analysis.

For the LC methods, a reverse phase method (flow rate: 0.200 mL/min, 80.0% methanol balanced with 0.1% formic acid in water, 8 min) and a C-18 HPLC column (Synergi 4μ fusion-RP 80A, 100*2 mm) were used for analysis. The following parameters were used for the MS analysis: curtain gas, 14 psi; nebulizer gas (gas 1), 14 psi; CAD gas, 4 psi; TurboIonSpray (IS) voltage, 4,500 V; entrance potential, 10 V; declustering potential, 30 V. collision energy, 19 eV, collision cell exit potential, 15 V, for m/z: 331.3→313.1 (7-OH-CBD); collision energy, 29 eV, collision cell exit potential, 8 V for m/z 345.3→299.1 (7-COOH-CBD); source temperature, 400°C; and dwell time, 50 ms. The instrument parameters and the ion transitions were verified with the injection of 1,000 ng/mL pure standard diluted in 50:50 methanol:water for each analyte. The pooled plasma which was spiked with commercially available standards was used for calibrating the MS/MS method, preparing for the standard curve from 12.5 ng/mL to 800 ng/mL for 7-OH-CBD and 125–8,000 ng/mL for 7-COOH-CBD.

PK Analysis

The PK of CBD, 7-OH-CBD, and 7-COOH-CBD were evaluated using non-compartmental analysis with SAS® 9.4 (Cary, NC, USA). Peak concentration (C_{max}) and the time to C_{max} (T_{max}) were reported as observed. The area under the plasma concentration-time curve from time 0–8 h (area under the curve [AUC]) for these single dose assessments were calculated according to the linear trapezoidal rule. Metabolite-to-parent drug exposure ratio (MPR) was calculated by dividing the AUC of 7-OH-CBD and 7-COOH-CBD with CBD AUC, respectively [17].

Statistical Analysis

The statistical analysis was performed with GraphPad Prism 9 and SAS® 9.4. One-way analysis of variance was applied to AUC and C_{max} with sex and race. Linear regression analysis was provided to identify the correlations of AUC and C_{max} to BMI and body weight. For the analysis of sex differences, C_{max} and AUC were normalized by body weight. Multiple t tests were performed to the plasma concentrations of each time point for males and females.

Results

Demographic Data for Test Subjects

The study included a total of 12 healthy volunteers (6 men and 6 women) aged 21–44 years (26.7 ± 6.5 years; weight, 65.8 ± 14.1 kg; mean ± SD) with a mean BMI of 23.04 (range: 18.50–27.60). The demographic characteristics of the study participants are presented in Table 1.

PK of CBD, 7-OH-CBD, and 7-COOH-CBD

For CBD, T_{max} is 4 [1–6] h (median [min–max]), C_{max} is 389.17 ± 153.23 ng/mL (mean ± SD), and AUC is 1,542.19 ± 488.04 ng/mL*h (mean ± SD). For 7-OH-CBD, T_{max} is 4 [2–6] h (median [min–max]), C_{max} is 81.35 ± 36.64 ng/mL (mean ± SD), AUC is 364.70 ± 105.59 ng/mL*h (mean ± SD), MPR is 0.25 ± 0.07 (mean ± SD). For 7-COOH-CBD, T_{max} is 4 [1–6] h (median [min–max]), C_{max} is 1,717.33 ± 769.22 ng/mL (mean ± SD), AUC is 9,888.42 ± 3,961.47 ng/mL*h (mean ± SD), MPR is 7.11 ± 3.48 (mean ± SD). The plasma concentration versus time after the last dose is shown in plot Figure 2, and the PK results are listed in Table 2. One-way analysis of variance identified the higher C_{max} and AUC of 7-COOH-CBD in female subjects with the normalization of body weight.

For 7-COOH-CBD, female subjects had an average C_{max} value of 2,195.00 ± 778.71 ng/mL. Male subjects had an average C_{max} value of 1,239.67 ± 384.38 ng/mL.

Table 1. Demographic data for participants

Race	Sex		Age, years	Weight, kg	Height, cm	BMI, kg/m^2
Mixed Race	Female		31	53.00	160.00	20.70
Asian	Female		44	51.60	157.00	20.90
White	Female		25	59.00	174.50	19.40
Asian	Female		21	66.90	155.60	27.60
Native American	Female		29	53.10	154.10	22.40
White	Female		21	56.90	169.20	19.90
		Mean±SD in females	29±9	56.75±5.69		
Black	Male		30	60.30	161.00	23.30
White	Male		27	79.20	170.00	27.40
White	Male		23	78.50	185.30	22.90
White	Male		22	90.00	180.90	27.50
White	Male		21	54.20	171.30	18.50
Asian	Male		26	87.10	183.00	26.00
		Mean±SD in males	25±4	72.44±14.76		
		Mean	27	65.82	168.49	23.04
		Maximum	44	90.00	185.30	27.60
		Minimum	21	51.60	154.10	18.50
		Standard deviation	7	14.14	10.98	3.34

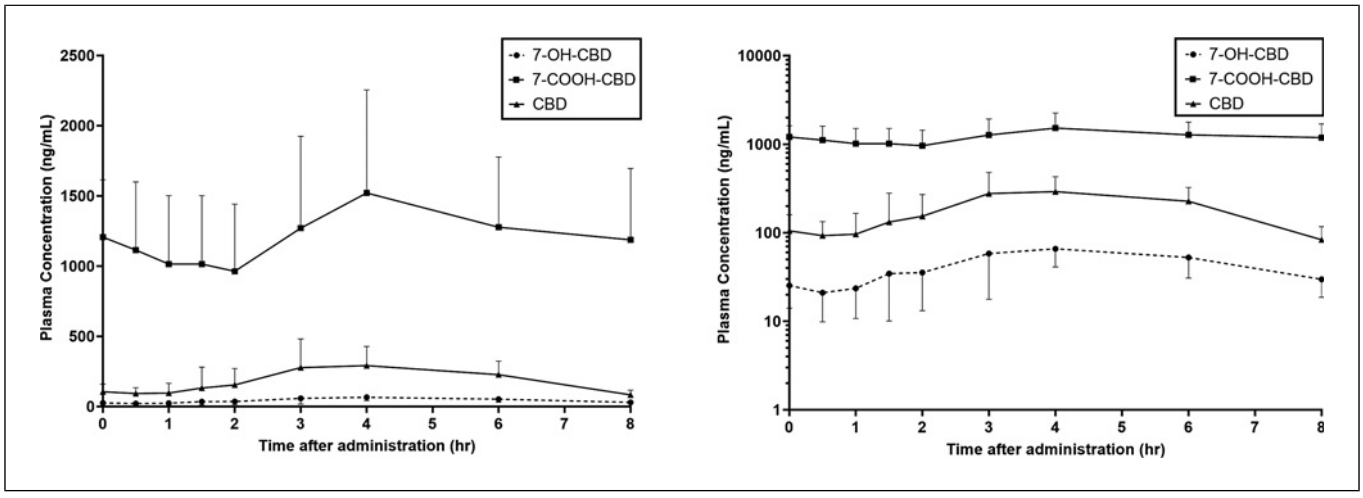

Fig. 2. Plasma concentration versus time curve for CBD, 7-OH-CBD, and 7-COOH-CBD. Left: linear scale, right: log scale. Error bars represent standard deviation.

Female subjects had an average AUC value of 12,033.00 ± 4,114.88 ng/mL*h, while male subjects had an average AUC value of 7,743.83 ± 2,560.23 ng/mL*h.

With consideration to the usual weight difference between male and female subjects, the C_{max} and AUC were normalized for body weight. For 7-COOH-CBD, female subjects had an average C_{max} value of 39.81 ± 16.77 ng/mL/kg body weight. Male subjects had an average C_{max} value of 17.69 ± 8.06 ng/mL*h/kg body weight. Finally, female subjects had an average AUC value of 217.70 ± 88.18 ng/mL*h/kg body weight, while male subjects had an average AUC value of 110.70 ± 52.25 ng/mL*h/kg body weight.

Table 2. Non-compartmental analysis for CBD, 7-OH-CBD, and 7-COOH-CBD

Compound	Parameters	Mean±SD	Lower 95% CL for mean	Upper 95% CL for mean	Minimum	Maximum
CBD	T_{max}, h*	4±1.62	3.05	5.11	1.00	6.00
	C_{max}, ng/mL	389.17±153.23	291.81	486.52	177.00	648.00
	AUC, ng/mL*h	1,542.19±488.04	1,232.10	1,852.28	737.30	2,331.00
7-OH-CBD	T_{max} (h)*	4±1.42	3.35	5.15	2.00	6.00
	$C_{max,}$ ng/mL	81.35±36.64	58.07	104.63	30.00	173.00
	AUC, ng/mL*h	364.70 ± 105.59	297.61	431.79	188.10	554.20
	MPR	0.25±0.07	0.20	0.29	0.16	0.36
7-COOH-CBD	T_{max}, h*	4±1.50	3.38	5.28	1.00	6.00
	C_{max}, ng/mL	1,717.33±769.22	1,228.59	2,206.07	813.00	3,100.00
	AUC, ng/mL*h	9,888.42±3,961.47	7,371.42	12,405.42	4,890.00	18,143.00
	MPR	7.11±3.48	4.90	9.32	2.52	13.74

*T_{max} is shown as the median.

There was a statistically significant (p = 0.0155) difference in the normalized C_{max} between male and female subjects, with female subjects having a 2.25-fold higher average normalized C_{max} than the male subjects. There was also a statistically significant (p = 0.0285) difference of the normalized AUC between male and female subjects, with female subjects having a 1.97-fold higher average normalized AUC than the male subjects (shown in Fig. 3).

Multiple t tests identified a statistically significant difference (p = 0.0262) plasma 7-COOH-CBD concentration at the 4 h time point after the last administration of CBD in male and female subjects (shown in Fig. 4).

Linear Regression Identified a Significant Linearity of the 7-OH-CBD AUC in Female Subjects

The analysis of linear regression showed a significant correlation between AUC and body weight in female subjects (r^2 = 0.8165, p = 0.0135). The derived linear model for this relationship is expressed as AUC = −20.24 * Weight +1,545. No significant linear relationship was observed between body weight and male subjects. Additionally, the linear regression for C_{max} in relation to body weight indicates a stronger correlation in females (r^2 = 0.5452) compared to males (r^2 = 0.1979), though it does not reach the statistical significance (p = 0.0937) (shown in Fig. 5).

Discussion

An understanding of the PK of CBD and its major metabolites is crucial in assessing the therapeutic effects and potential side effects of CBD administration in clinical settings. An appreciation of these parameters is also potentially important relative to dosing considerations and differential response. Although the pharmacology of CBD and its derivatives has been well studied, it remains incompletely understood. In the CNS, CBD does not bind appreciably to CB1 and CB2 receptors, unlike THC, which is an agonist of these receptors [18]. Pharmacological studies suggest that CBD acts as a negative allosteric modulator of CB1 receptors [6]. This indicates a longer action and structural modification by CBD in the CNS. The overall biological function of CB receptors in CNS is not well understood. Animal studies suggest that activation of CB receptors may alter dopamine release in the reward system [19], which is related to biological functions such as food intake, learning, sexual behaviors, and multiple neurological disorders, including Parkinson's disease and depression [20]. The biological consequences of CB receptor activation and regulation still require further study. The major 7-OH-CBD metabolite has similar biological effects to the parent drug in both the CNS and periphery [21]. At present, 7-COOH-CBD is considered a pharmacologically inactive metabolite due to its lower lipid solubility and uncertainties regarding its transport across the blood-brain barrier [22]. However, in vitro research suggests that 7-COOH-CBD has a higher binding affinity for peripheral CB1 receptors compared to CBD [21], supporting further investigations into the biological activities of 7-COOH-CBD in the periphery.

Although CBD appears to be a relatively safe drug for clinical use, its associated side effects and potentially those of its metabolites must be considered. In human studies for epilepsy and psychiatric disorders, CBD has

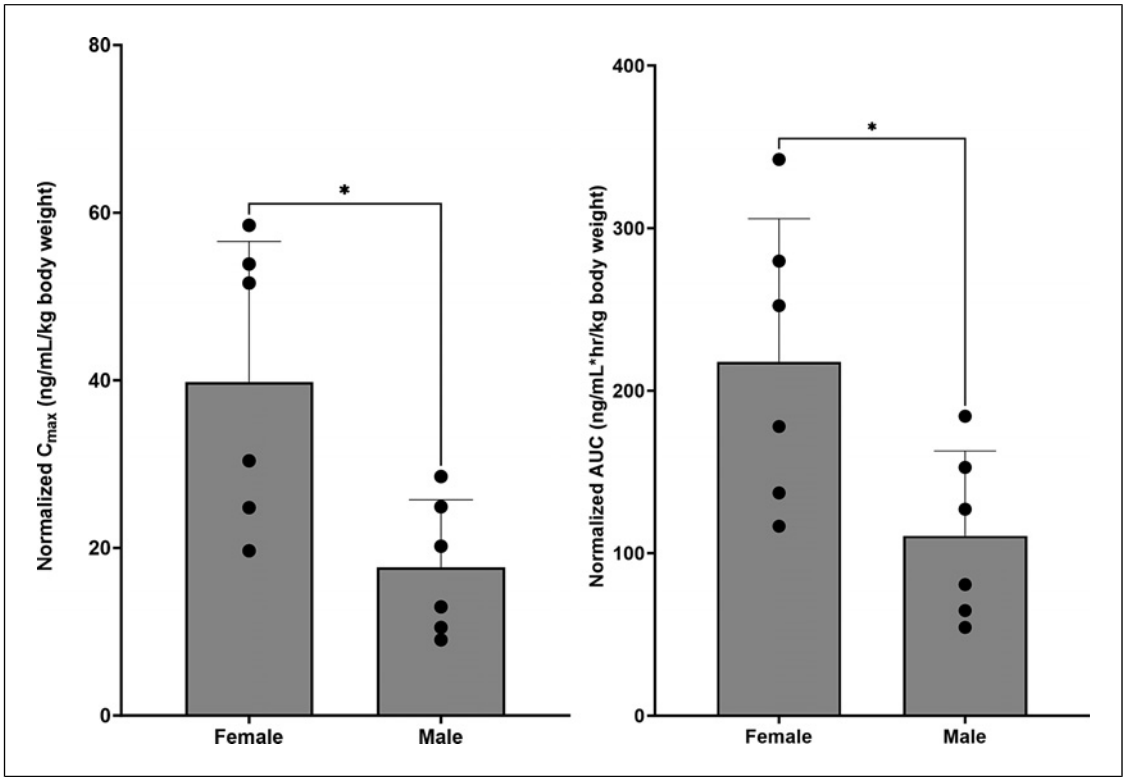

Fig. 3. A *t* test identified a significantly higher normalized C_{max} ($p = 0.0155$) and AUC ($p = 0.0285$) of 7-COOH-CBD in female subjects. Error bars represent standard deviation.

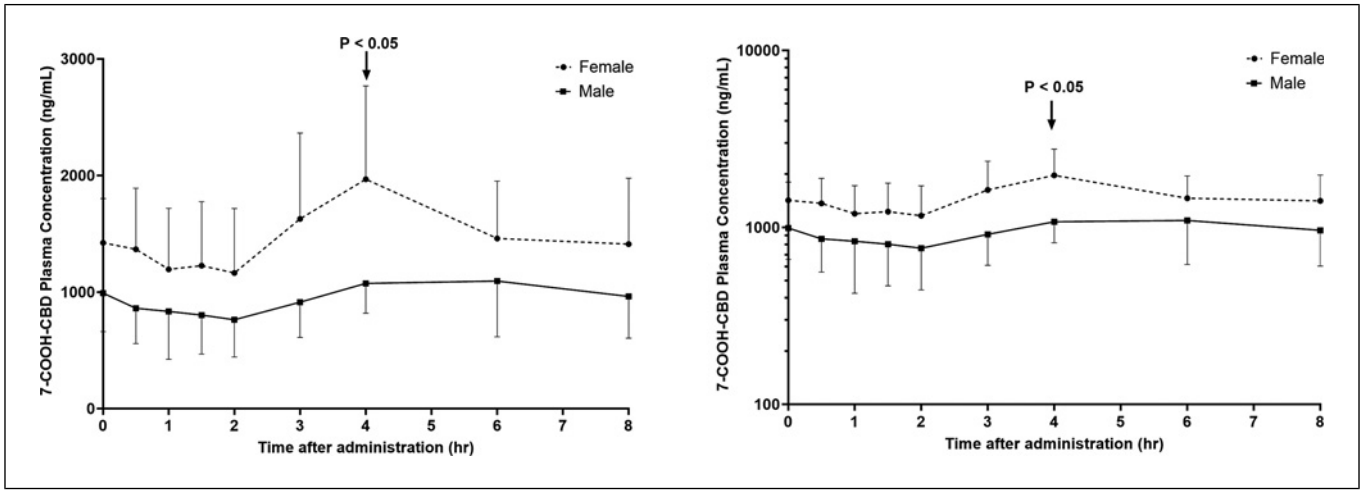

Fig. 4. Plasma concentration of 7-COOH-CBD in male versus female subjects. Left: linear scale, right: log scale. Multiple *t* tests were performed on all individual time points. $p = 0.0262$ at 4 h. Error bars represent standard deviation.

been variously reported to cause hepatic abnormalities, diarrhea, fatigue, vomiting, and somnolence in some subjects [23]. Additionally, in vitro studies show an inhibition of CBD and its major metabolites on selected CYP enzymes [24] and CES1 [25], which may pose some potential liability for drug-drug interactions.

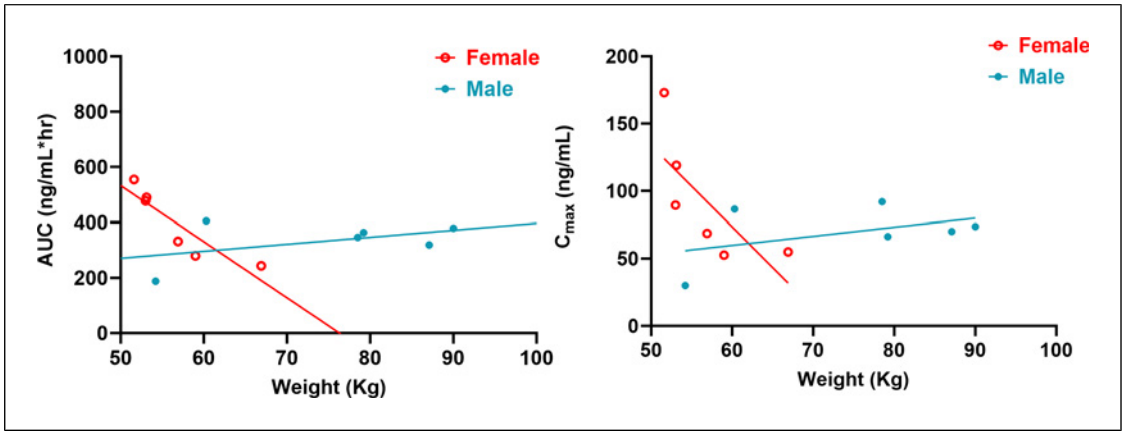

Fig. 5. Linear regression of body weight and AUC and C_{max} in male and female subjects. Left: AUC versus body weight. For female, $r^2 = 0.8165$, $p = 0.0135$. For male, $r^2 = 0.2260$, $p = 0.3407$. Right: C_{max} versus body weight. For female, $r^2 = 0.5452$, $p = 0.0937$. For male, $r^2 = 0.1979$, $p = 0.3767$.

Consistent with other clinical studies of CBD and its major metabolites [11, 16, 26, 27], results of this study showed that 7-COOH-CBD attains the highest plasma concentration, followed by the parent drug CBD, with 7-OH-CBD having the lower concentration. Similar to the report by Schultz et al. [12], the significant differences in AUC, C_{max} for CBD with respect to race, sex, age, or BMI were unable to be identified. Additionally, no significant differences were identified in C_{max} and AUC of CBD and 7-OH-CBD when analyzing age, sex, and BMI. There was no significant difference in C_{max} and AUC for 7-COOH-CBD concerning age and BMI. Published clinical studies have reported that the absorption and elimination of CBD vary depending on the formulation, dose, and fasting conditions [11]. However, unlike the parent drug, the formation and metabolism of secondary and tertiary metabolites are largely dependent on the metabolic activity of individual subjects, so their effects are likely to be more pronounced than those of the parent drug. For 7-COOH-CBD, a 2.25-fold higher C_{max} and 1.97-fold higher AUC for female subjects after normalizing body weight. These results are consistent with recently published clinical research by MacNair et al. [28] on the administration of cannabis oil. The reason for the sex difference in C_{max} and AUC is unclear, but it could be due to sex differences in UGT activity. As the terminal metabolite of the phase I reaction, 7-COOH-CBD is further metabolized through glucuronidation and eliminated by the renal system [22]. Previous research has reported sex differences in UGT activity, such as slower UGT2B15 metabolism in females [29], which may contribute to the observed PK differences between male and female subjects for 7-COOH-CBD.

In the treatment of seizure disorders, the dose of CBD in clinical practice is based on the patients' body weight. However, in the context of this study, a fixed CBD dose (i.e., 750 mg twice daily) was administered to all participants, irrespective of their body weight. Interestingly, the results revealed that there was no noteworthy linear relationship observed between the body weight and the C_{max} and AUC of CBD. Significant linear correlations between 7-OH-CBD AUC and body weight were observed among females, whereas such correlations were not found to be significant in males. This trend is also mirrored in the C_{max} results for females, although statistical significance was not reached. There were no substantial linear associations observed in CBD and 7-COOH-CBD C_{max} and AUC with body weight. The underlying reason for this finding remains uncertain, although it might be attributed to the difference in fat tissue distribution between females and males. Females tend to have a greater proportion of fat tissue, leading to an increased volume of distribution for lipid-soluble drugs [30]. Consequently, this higher volume of distribution potentially contributes to lower AUC and C_{max} values for 7-OH-CBD.

There are several limitations of the study. First, as previously noted in the background, the investigation into CBD and metabolite PK utilized samples from a prior CBD-MPH drug interaction assessment. Following the administration of CBD at 750 mg twice daily for 3 days, subjects were given a single 10 mg dose of immediate-release MPH on the 4th day concurrently with a final 750 mg dose of CBD. Although MPH is not recognized as a significant metabolic inhibitor of any drug-metabolizing enzyme and has a relatively short half-life

(2–3 h), there nonetheless exists the possibility of some minor metabolic effect that all subjects might have experienced. Secondly, the half-life of orally administered CBD has been reported to range from 14.43 to 60.54 h at varying dosages [13]. This variability makes it challenging to ensure that all subjects had attained a steady state by the 4th clinical day. A pharmacokinetic study of a more extended duration may be warranted to validate the results from the current study. Third, the sample size in the current study (6 women, 6 men) is insufficient to draw statistically reliable conclusions to represent a large population. It was noted that the normalized C_{max} for 7-COOH-CBD displayed two distinct clusters in women, with no significant differences observed by race, BMI, or body weight. The reason for these separated clusters is unknown, and it may be attributed to the variability and limited sample size. Likewise, conclusive statements about different race and ethnicities are not drawn due to the small sample size. A larger population PK study is necessary to validate the results of the current study.

Conclusion

In this study, no significant differences were identified in C_{max} and AUC of CBD and the MPR of active metabolite 7-OH-CBD when analyzing with sex, race, and BMI. Additionally, there were no significant differences in C_{max} and AUC for 7-COOH-CBD concerning race and BMI. A 2.55-fold higher C_{max} (p = 0.0155) and 1.97-fold higher AUC (p = 0.0285) for female subjects for the inactive metabolite, 7-COOH-CBD. A significant linearity (p = 0.0135) of 7-OH-CBD AUC with body weight in females was observed. However, confirmation of these observations requires further investigation utilizing a larger study population.

Acknowledgments

Epidiolex® was generously donated by Greenwich Biosciences, Inc. for the original drug interaction assessment study which served as the source for study plasma samples.

Statement of Ethics

The study protocol and informed consent document, inclusive of Health Insurance Portability and Accountability Act language, were approved by the University of Florida Investigational Review Board (NCT04603391). All subjects provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study design: Q.Z., J.S.M.; experimental design, analysis of data, and preparation of the manuscript: Q.Z., J.S.M., and P.W.M.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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