Supplementary Data

Supplementary Material

To participate, volunteers had to satisfy the following inclusion criteria: participants had to be males or nonpregnant females between 18 and 55 years of age and nonsmoking, occasional cannabis consumers (less than once a month). Their body mass index had to be between 18.5 and 30.0 kg/m^2 and be considered healthy according to their medical history, ECG, vital signs, laboratory results, and a physical examination as determined by the principal investigator. Participants had to be able to comprehend the nature of the study, provide written informed consent, and be able to fast for at least 14 hours. Individuals were excluded from participating if they had a known history or presence of clinically significant hepatic, renal/genitourinary, gastrointestinal, cardiovascular, cerebrovascular, pulmonary, endocrine, immunological, musculoskeletal, neurological, psychiatric, dermatological, or hematological disease or condition, as well as any clinically significant illness within 30 days of the first dosing. A positive test result for HIV, substance of abuse, alcohol, Hepatitis B surface antigen and/or C, and pregnancy and/or breastfeeding for females or the use of any enzyme-modifying drugs or products, including cytochrome P450 (CYP450) enzymes, and strong inducers of CYPP450 enzymes within 30 days before first drug dosing also resulted in exclusion from the study.

For the 5 mg treatment arms, 1 × 5 mg Δ^9-tetrahydrocannabinol (THC) and 1 placebo was administered under a fasting condition (Treatment A: 5 mg THC fasted) or after a high-fat meal (Treatment B: 5 mg THC + high-fat meal). For the 10 mg treatment arms, 2 × 5 mg THC was administered under a fasting condition (Treatment C: 10 mg THC fasted) or after a high-fat meal (Treatment D: 10 mg THC + high-fat meal) (Table 1). There was at least a 7-day washout period between study intervals (crossover design). Blood samples were collected before the THC dose and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, and 24 hours in each study period.

Randomization was generated by a computer program designed and run in SAS® Version 9.4 at Biopharma Services, Inc. Four different sequences for randomization were used. Clinical staff and participants were blinded to the randomization sequence and administered dosages (double blinded).

Upon check in for each study period, urine samples were collected from participants to test for cannabis, nicotine, and alcohol use. Female participants also had urine human chorionic gonadotropin levels tested. Only participants who tested negative for these tests were allowed to participate in the study.

Participants were unable to leave the clinic at least 10.5 hours before dosing for a minimum of 24 hours postdose (a total of 34.5 hours) for each study interval. Water was provided *ad libitum* except for the hour before and the hour following dosing when water was not permitted. Capsules were taken with 240 mL of water and three standardized meals (Supplementary Table S1) were provided at hour 4.5, 9.5, and 13.5

Supplementary Table S1. The Meals Participants Were Provided After They Had Consumed Their Capsules

Time point	Measurements	Contents
Hour 4.5	140 g	Seasoned Basa
	36 mL	Tartar sauce
	224 g	Basmati rice with vegetables (peas and carrots)
	84 g	Roasted vegetables (onions, zucchini, green peppers, red peppers)
	250 mL	Potato leak soup
	1 pk of 2	Crackers
	112 g	Fruit salad (no grapefruit or pomelo)
	341 mL	Minute maid apple juice
Hour 9.5	100 g	Chicken Kafta
	224 g	Vegetable rice with peas, carrots, and onions
	35 mL	Tzatziki sauce
	84 g	Greek salad (iceberg lettuce, onions, tomatoes, cucumbers, olives, fetta cheese)
	32 mL	Greek dressing
	112 g	Red grapes
	341 mL	Minute Maid cranberry juice
Hour 13.5	140 mL	Yogurt parfait with fresh fruit and granola on the side
	32 g	Whole wheat bagel
	28 g	Cream cheese
	500 mL	Water

Supplementary Table S2. Definitions of Adverse Events

Adverse event	Definition
Mild	Adverse event resulting in discomfort, but not sufficient to cause interreference in normal daily activities
Moderate	Adverse event resulting in discomfort that is sufficient to cause interference in daily activities
Severe	Adverse event resulting in discomfort causing an inability to carry out normal daily activities

postdose for all treatment groups. Alcohol consumption and products containing caffeine/methylxanthines and poppy seeds were prohibited 48 hours before dosing until the last blood draw of each interval. Cannabis products were not permitted for 14 days before the first dosing. Participants were required to stay awake and upright with limited activity for the first 4 hours after dosing and then allowed to move freely, except for vigorous activity, until 24 hours.

For the fasting periods, no food was allowed at least 10 hours before dosing and at least 4 hours after dosing. For the high-fat meal groups, no food was allowed for at least 10 hours before the high-fat, high-calorie breakfast, which was taken 30 minutes before dosing and had to be consumed within 30 minutes. The high-fat, high-calorie breakfast is outlined in Table 2.

Systolic blood pressure, diastolic blood pressure, and heart rate were monitored predose and at 1, 2, 4, 12, and 24 hours postdose in each period. The reported adverse events were classified as either mild, moderate, or severe, definitions of which can be found in Supplementary Table S2.

The digit symbol substitution test (DSST), adapted from the Wechsler Adult Intelligence Scale (WAIS),[S1] was administered at predose and then 1, 2, 3, and 6 hours postdose to assess cognitive performance. During the DSST, participants were presented with a cipher that linked nine digits (1–9) with nine corresponding symbols and then provided a list of digits with blanks below, in which to fill the corresponding symbol. Participants were asked to complete as many substitutions as possible in a 90-second time span. The number of substitutions completed and the number of incorrectly completed substitutions were recorded for each patient.

Analytical procedure for THC

Blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C within 30 minutes of collection. After centrifugation, two 1 mL aliquots of plasma were transferred to chilled polypropylene tubes containing 100 μL of 10% ($v \cdot v^{-1}$) phosphoric acid and stored in a freezer at –20°C. Plasma samples were analyzed using reverse-phase liquid chromatography. The analyte and internal standards were detected using tandem MS detection. The study was performed using a Triple Quad API 5000, 5500, and 6500 $LC \cdot MS^{-1} \cdot MS^{-1}$ system with a Turbo Ion spray interface. The negative ions were measured in MRM mode. Data were acquired and analyzed by Applied Biosystems "Analyst" software, versions 1.5, 1.5.2, 1.6, and 1.6.2. The Lower Limit of Quantitation for THC was 93.750 $pg \cdot mL^{-1}$ and the Upper Limit of Quantitation for THC was 10000.000 $pg \cdot mL^{-1}$.

Noncompartmental analysis

Noncompartmental analysis was performed using NCAR in R3.5.2. Automatic slope selection with the same $r > 0.9$ and AUC using log-linear trapezoidal rule was performed.[S2] This analysis was done external to MedReleaf® and Aurora Cannabis, Inc®.

Statistical analysis

Results are stated as mean ± SD and the data was analyzed external to MedReleaf and Aurora Cannabis, Inc. Statistical comparisons were made using R3.52 for one-way ANOVA for pharmacokinetic parameter analysis, with a *post hoc* Bonferroni Test if the F was significant and no significant variance in homogeneity, and Student's t-test for demographic characteristics. GraphPad Prism 8 was used to generate graphs and Kruskal–Wallis H test for analysis of the DSST data. Statistical significance was determined as $p < 0.05$.

Materials

THC hard gelatin capsules were obtained from MedReleaf, a Canadian Licensed Producer of medical cannabis. Whole *Cannabis sativa* plant extract was dissolved in sunflower oil and encapsulated in hard gelatin capsules. Each capsule contained 5.4 mg THC, 0.2 mg THCA, <0.1% $wt \cdot wt^{-1}$ terpenes, and no detectable cannabidiol or cannabidiolic acid.

Supplementary References

S1. Matarazzo JD, Herman DO. Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. J Clin Neuropsychol. 1984;6:351–366.

S2. Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis: concepts and applications. Swedish Pharmaceutical Press: Stockholm, Sweden, 2017.