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ORIGINAL RESEARCH

Examination of a New Delivery Approach for Oral Cannabidiol in Healthy Subjects: A Randomized, Double-Blinded, Placebo-Controlled Pharmacokinetics Study

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ABSTRACT

Introduction: Therapeutic effects of cannabidiol (CBD) in specialized populations continue to emerge. Despite supra-physiological dosing being shown to be tolerable in various pathologies, optimization of CBD absorption has obvious benefits for general health and recreational usage. Our objectives were to: (1) to investigate a joint pharmacokinetic-physiological time course of multiple recreational-equivalent (< 100 mg) dosages of oral CBD in young healthy adults and (2) evaluate a newly developed technology (TurboCBD^{TM}) for the enhanced delivery of CBD.

Methods: In a double-blinded, placebo-controlled, cross-over design, 12 participants received placebo, generic 45 or 90 mg of CBD, or TurboCBD^{TM} delivery technology capsules on five separate occasions.

Results: Although there were no differences in the 45 mg conditions, circulating CBD levels were higher with the TurboCBD^{TM} 90 mg group at both 90 (+ 86%) and 120 (+ 65%) min compared with the 90 mg control ($p < 0.05$). Total area under the curve tended to be higher with TurboCBD^{TM} 90 mg compared with 90 mg (10,865 ± 6322 ng ml^{-1} vs. 7114 ± 2978 ng ml^{-1}; $p = 0.088$). Only the TurboCBD^{TM} 90 mg dose was elevated greater than placebo at 30 min ($p = 0.017$) and remained elevated at 4 h ($p = 0.002$).

Conclusion: Consistent with higher bioavailability, TurboCBD^{TM} 90 mg at the peak CBD concentration was associated with an increase in cerebral perfusion and slight reduction in blood pressure compared with baseline and the 90 mg control. Further studies are needed to establish the mechanisms of action of this technology and to explore the therapeutic potential of acute and chronic dosing on more at-risk populations.

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INTRODUCTION

Cannabidiol (CBD) is a bioactive cannabinoid in marijuana (*Cannabis sativa*). Unlike the other common cannabinoid compound, Δ^9 tetrahydrocannabinol (THC), CBD lacks appreciable affinity or activity at the cannabinoid receptors (CB_1 and CB_2) and therefore lacks the psychoactivity of the archetypal cannabinoid [1]. Available evidence suggests that there are marked therapeutic CBD effects for diverse disease processes including inflammation and cancers [2], psychosis (e.g., [3]), schizophrenia [4] and epileptic seizures [1]. Moreover, it has been reported that CBD administration may improve cognitive performance in preclinical models of cognitive impairment, but not in healthy individuals (reviewed in: [5, 6]); due to the less influential distribution of cannabinoid receptor densities in the cerebellum, motor performance may not be impacted by CBD [7] and CBD may actually have subjective anxiolytic properties [8–10].

Although the safety and pharmacokinetics of oral CBD at high doses (400 and 800 mg) have been established [11], the study was conducted in combination with intravenous fentanyl. The only studies to investigate the pharmacokinetics and tolerability of oral CBD in healthy humans have been recently published [12]. The first study was an FDA-approved formulation of CBD (Epidiolex®) in healthy volunteers; in three different interventions, the volunteers were provided with doses between 1500 and 6000 mg once or twice a day [12]. The findings revealed that after single oral doses, the time to maximum plasma CBD concentration was approximately 4–5 h and the plasma concentration-time curve occurred in a non-significant and non-dose-proportional manner [12]. While these data have obvious clinical implications, the employed CBD dosing was an order of magnitude higher than is commonly used on a recreational/supplemental basis, e.g., 15–100 mg vs. > 1000 mg. In the second study, Atsmon and colleagues recently evaluated 10 mg and 100 mg CBD doses bound to gelatine matrix pellets. These results revealed a maximum plasma CBD concentration occurred within 3–3.5 h and an improvement in total absorption versus a reference 10 mg CBD oromucosal spray [13]. In alignment with means to optimize lower quantity dosages, the absorption of CBD, and consequently the altered pharmacokinetics over multiple 'recreational' doses in healthy humans, is important and largely unexplored [14].

In a randomized, double-blinded, placebo-controlled design, the purpose of this study was to examine the pharmacokinetics, metabolic and haemodynamic responses of oral CBD in healthy volunteers. Additionally, we evaluated a recently developed, patented capsule formulation (TurboCBD™; Lexaria Bioscience Corp., Canada), which was postulated to result in a more rapid appearance and higher concentrations of CBD in the blood than a concentration-matched control capsule formulation without the TurboCBD™ enhancement.

METHODS

Participants

Thirteen healthy young males were recruited, and 12 (24 ± 4 years; 83 ± 10 kg; 182 ± 5 cm; 25 ± 2 kg/m^2) completed all experimental sessions. The only participant to drop out did so after the first visit because of the inability to attend all sessions. Exclusion criteria included obesity (body mass index > 30 kg/m^2), hypertension (systolic > 130 mmHg; diastolic > 85 mmHg), diabetes, history of smoking, medicinal/recreational use of cannabis, opioid use or known intolerance to ginseng or ginkgo herbals. In addition, participants were excluded if they had any previous history of cardiopulmonary, liver, gastrointestinal (GI), kidney or cerebrovascular diseases, clinically diagnosed anxiety or depression or if they were taking

prescription drugs or over-the-counter supplements. Approval of this study was obtained by the Ethics Committee at the University of Split School of Medicine, and all procedures conformed to the Declaration of Helsinki. All participants provided written informed consent prior to completion of any data collection.

Experimental Design

The double-blinded, placebo-controlled, crossover study involved participants attending the laboratory on five separate occasions, separated by at least 6 days. Each visit was identical in the timing of blood sampling and physiological measures; only the supplementation differed. To avoid any potential confounding influence of diurnal variations, participants began testing on each visit at approximately the same time (within 1–2 h). Participants were allowed a light, low-fat breakfast 1–2 h prior to reporting to the laboratory each the morning. Water was permitted ad libitum, and a standardized snack was allowed at 4 h after the respective measurements. During each visit, participants were asked to replicate their diets for the preceding 24-h and avoid alcohol, caffeine and strenuous exercise for 12-h before each visit. Dietary logs were collected and confirmed at the start of each visit. Upon arrival each morning, participants provided a urine sample and then lay semi-supine (upper body tilted at 30° incline) for at least 10 min before an indwelling intravenous catheter was inserted into the medial antecubital vein for repeated blood sampling. Cardiorespiratory measures (see below) and blood sampling were repeated at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h. Urine was collected at baseline and at 3 and 6 h to evaluate CBD urinary excretion. Tests of cognitive function and subjective questionnaires were made at baseline and around 1.5 and 3 h. Finally, other basic haematological and inflammatory parameters were also measured at baseline, 1.5 and 3 h; these included haemoglobin, haematocrit, white blood cells, red blood cells, platelets, glucose, insulin, erythrocyte sedimentation rate and C-reactive protein. These procedures are detailed below.

Cardiorespiratory Measures

Blood pressure and heart rate were collected in triplicate from the brachial artery using an automated sphygmomanometer (Omron Healthcare, Japan), with the mean of the two most repeatable measurements used for data analysis. Respiratory rate and end-tidal PCO_2 were collected using a capnograph (EMMA, Masimo, USA) for an evaluation of velocity independent of end-tidal PCO_2. Cerebral perfusion was indexed via blood velocity in the right middle cerebral artery (MCAv) and left posterior cerebral artery (PCAv) and was measured using a 2-MHz transcranial Doppler ultrasound (TCD; Spencer Technologies, Seattle, WA, USA). The TCD probes were attached bilaterally to a specialized commercial headband (model M600 bilateral head frame, Spencer Technologies, Seattle, WA, USA) and secured in place. Insonation of the MCA and PCA was performed through the trans-temporal window using the previously described location and standardization techniques, in accordance with current guidelines [15].

Cognitive Function and Subjective Questionnaires

Cognitive performance was assessed using Cogstate software (Cogstate Ltd., Melbourne VIC, Australia)—an automated and standardized battery of cognitive tests performed on a computer [16]. The cognitive test selected was the "two back test" to assess working memory. Each test required the participant to respond to playing cards that turned over one card at a time; all tests calculated both reaction time and accuracy performance scores. The two-back test required the participant to respond either "yes" or "no" depending on whether the playing card was the identical card shown two cards previously. Participants were familiarized before each experimental session. A 10-point visual analogue score was used to assess GI distress/hunger [17].

Supplementation and Dosing

Each participant received in a randomized and double-blinded order: placebo control capsules; 45 mg CBD encapsulated as TurboCBD^{TM} (45 mg CBD; 600 mg American ginseng; 240 mg ginkgo biloba; 150 mg organic hemp oil); 45 mg

CBD via generic CBD capsules (45 mg CBD via 150 mg organic multi-spectrum hemp oil); 90 mg CBD encapsulated as TurboCBD^{TM} (90 mg CBD; 1200 mg American ginseng; 480 mg ginkgo biloba; 300 mg organic hemp oil); 90 mg CBD via generic CBD capsules (90 mg CBD via 300 mg organic multi-spectrum hemp oil). The active capsules were formulated using organic, multi-spectrum hemp CO_2 extract (sourced from Endoca, San Diego, CA, USA), and the number of pills consumed on each visit was identical. The TurboCBD^{TM} capsules incorporate DehydraTECH^{TM} delivery technology, which includes a patented process by which long-chain fatty acids, high in oleic acid, are associated through a dehydration process procedure with the CBD. It is believed that this proprietary process assists the human GI system in uptake of the CBD via bypassing (or reducing) first-pass liver metabolism; therefore in the short term, it was speculated that this approach allows for higher volumes of CBD to enter the circulatory system in a more rapid fashion, circumventing first-pass liver metabolism than what is otherwise achieved with generic forms of CBD.

Sample Collection, Analysis and Storage

Blood samples (10 ml each) were collected in lithium heparin and K2EDTA vacutainers. Within 30 min of collection, plasma was separated (centrifuged at 4 °C on 3500 rpm for 10 min) and stored at − 20 °C. The plasma samples (1.5–2 ml each) and three urine samples (5 ml) were used for further analysis.

Standard Solution

Cannabidiol standard solutions [tetrahydrocannabinol (THC); 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), 11-*nor*-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) and CBD, 1 mg ml^{-1} certified reference material; Lipomed AG, Switzerland] were prepared by dilution with methanol to a final concentration of 1 μg ml^{-1} and were used to prepare calibration samples. To establish linearity, a calibration curve was calculated by analysing drug-free plasma and urine samples spiked with: THC, 11-OH-THC and THCCOOH at concentrations of 5, 10, 50, 100 and 500 ng ml^{-1}; for CBD at concentrations of 2.5, 5, 10, 15, 25 and 50 ng ml^{-1}. The intra- and inter-assay coefficients of variation were < 10%.

Sample Extraction

Proteins in plasma and urine samples (1-ml aliquots) were precipitated with 1.25 ml ice-cold acetonitrile. After mixing, samples were centrifuged (2600 rpm for 2 min) and supernatant with 1 ml d.d. H_2O was added to preconditioned solid-phase extraction (SPE) columns with specific cartridges (United Chemical Technologies, Styre Screen SSTHC06Z; for both, plasma and urine extraction protocols were carried out according to the manufacturer's instructions). The column was rinsed with 1 ml d.d. H_20 and dried under high vacuum (∼ 20 inches). The samples were eluted with a 3-ml mix of hexane:ethyl acetate:acetic acid (49:49:2, v/v) and dried under nitrogen. Thereafter, the samples were reconstituted with 30 μl N,O-bis(trimethylsilyl) trifluoroacetamide with 1% trimethylchlorosilane (BSTFA) and derivatized for 0.5 h at 70 °C. Acetonitrile, hexane, ethyl acetate and acetic acid were purchased from Merck (Darmstadt, Germany).

GC-MS Analysis

The gas chromatography-mass spectrometry (GC-MS) analysis was performed on a Shimadzu GC/MS-QP2010 Ultra with a mass spectrometer detector (Shimadzu, Kyoto, Japan). The chromatographic column was InterCap 5MS/NP 5% phenyl, 95% methyl polysiloxane, length 30 m, diameter 0.25 mm and film thickness 0.25 μm (GL Sciences, Tokyo, Japan). The initial column temperature of 100 °C was held for 1 min, then ramped to 175 °C at 30 °C min^{-1}, then ramped again to 310 °C at 12 °C min^{-1} and held to the total run time of 15 min. Ultrapure-grade helium at the flow rate of about 1.5 ml min^{-1} was used as the carrier gas. Samples were injected using the splitless mode with an injection temperature of 250 °C. GC-MS analysis was performed using SIM mode with TMS characteristic ions. Detector voltage was in absolute

mode on 1.5 kV. Ion source temperature was 200 °C and interface temperature was 280 °C.

Pharmacokinetic (PK) Assessment

Peak plasma concentration (C_{max}), time to peak plasma concentration (time to C_{max}) and area under the curve (AUC) were calculated from each of the plasma concentrations. Plasma AUC was calculated by the following equation:

$$\text{AUC} = \sum_{t=0}^{n} (C_1 + C_2)/2 \times (t_2 - t_1)$$

where C_1 = concentration at time 1 (t_1) and C_2 = concentration at time 2 (t_2).

Haematological and Inflammatory Parameters

The whole-blood sample (K2EDTA) was processed immediately for haematological parameters (AcT 8 Haematology Analyzer, Beckman Coulter, Brea, CA, USA). These parameters included haemoglobin, haematocrit, white blood cell, red blood cell and platelet counts, mean corpuscular volume and mean corpuscular haemoglobin. The lithium heparin samples were centrifuged at 1550*g* for 10 min at room temperature to separate and freeze plasma at − 20 °C for future batch analysis. Plasma metabolic biomarkers (i.e., glucose and insulin; SST) were assessed using standard techniques at a clinical hospital laboratory using ELISA. Markers of inflammation were also quantified via erythrocyte sedimentation rate (4NC) and C-reactive protein (K2EDTA). The intra- and inter-assay coefficients of variation were < 10%.

Sample Size and Statistical Analyses

No prospective calculations of statistical power were made and the sample size was selected to provide information on pharmacokinetic and exploratory haemodynamic and metabolic parameters. Nevertheless, based upon previous studies investigating the effects of CBD on plasma concentrations and physiological outcomes (e.g., n = 4–10 [11, 12, 18]), a sample size of ten was deemed appropriate. Statistical analysis was performed using SPSS (version 24; IBM Corp., USA). Pharmacokinetics were analysed using a one-way ANOVA with post hoc Bonferroni correction. Blood pressure and cerebral artery velocity and conductance at peak concentration with 90 mg doses were evaluated using a paired Student's *t*-test. Haematological measures, urine and plasma CBD were evaluated using a linear mixed model, with dosage and time as factors and Bonferroni correction. Data are reported as mean ± standard deviation (SD), unless otherwise noted, and $p < 0.05$ was deemed statistically significant.

RESULTS

Tolerability and PK of Plasma CBD

There were no alterations in cognitive function (i.e., working memory), GI symptoms or reported anxiety in any of the experimental interventions or placebo trial (data not shown for simplicity). Figure 1 illustrates the dose- and time-dependent changes in plasma CBD concentration over 6 h. Total AUC plasma CBD

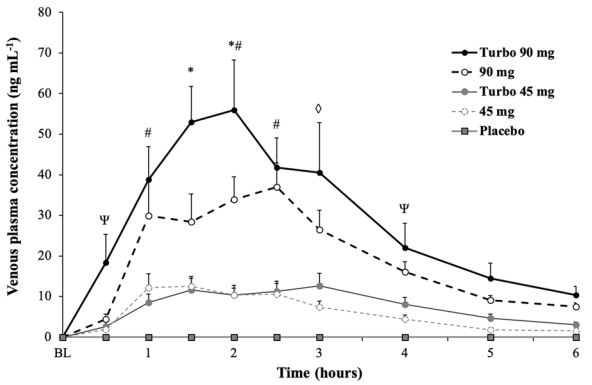

Fig. 1 Plasma cannabidiol (CBD) concentration in venous blood over 6 h following consumption of generic 45 mg (dashed grey open circles) and 90 mg (dashed black open circles) CBD doses compared to TurboCBD™ 45 mg (solid grey solid circles) and 90 mg (solid grey solid circles) CBD doses. Standard error included for clarity. $^{*}p < 0.05$ TurboCBD™ 90 mg > all others; $\#p < 0.05$ both 90 mg doses > both 45 mg doses others; $\lozenge p < 0.05$ TurboCBD™ 90 mg > both generic 45 mg doses; $\psi p < 0.05$ only TurboCBD™ 90 mg > placebo. Linear mixed model with Bonferroni correction

concentration was higher with the 90 mg dose (7115 ± 2978 ng ml^{-1}) compared with the 45 mg dose (2252 ± 1301 ng ml^{-1}; $p < 0.012$). Although there was no difference between the generic 45 mg and TurboCBD^{TM} 45 mg dose, there was a trend for total AUC with the TurboCBD^{TM} 90 mg dose (10,865 ± 6322 ng ml^{-1}) to be increased compared with the generic 90 mg dose (7114 ± 2978 ng ml^{-1}; $p = 0.088$; Table 1). Post hoc comparisons revealed that plasma levels with the TurboCBD^{TM} 90 mg dose were significantly higher than with the generic 90 mg at both 90 and 120 min (Fig. 1, $p < 0.01$). Furthermore, only the TurboCBD^{TM} 90 mg dose was elevated (i.e., greater than placebo) at 30 min ($p = 0.017$) and remained elevated (i.e., greater than placebo) at 4 h ($p = 0.002$). Plasma CBD or any of its metabolites were not detected on any days with placebo. Additionally, THC, 11-hydroxyl-THC and 11-nor-9-carboxy-THC (i.e., also referred to as THCCOOH) in plasma were all undetectable on any day.

Peak concentration (C_{max}), rate of absorption ($C_{BL\text{-}max}$) and rate of clearance ($C_{max\text{–}6h}$) were all higher with the 90 mg dose compared with the 45 mg dose ($p < 0.05$); however, no differences existed between TurboCBD^{TM} and generic CBD doses (Table 1). Although time to C_{max} and $C_{BL\text{-}max}$ was not different between 90 mg and TurboCBD^{TM} 90 mg (Table 1), when normalized to body weight, the AUC to C_{max} was highest with TurboCBD^{TM} 90 mg (35.3 ± 31.7 ng ml^{-1} kg^{-1}) compared with the generic 90 mg (15.3 ± 10.9 ng ml^{-1} kg^{-1}; $p = 0.039$; Fig. 2).

Peak (CBD) with Generic 90 mg Versus TurboCBD™ 90 mg

Blood Pressure

There was a tendency for MAP to be reduced at C_{max} with TurboCBD^{TM} 90 mg ($p = 0.098$), which appears more attributable to a change in diastolic blood pressure ($p = 0.092$). Similar changes did not occur with the generic 90 mg CBD dose (Table 2) or on placebo, which was time-synced to C_{max} of TurboCBD^{TM} 90 mg or generic 90 mg CBD, respectively.

Table 1 Plasma CBD concentration after generic 45 mg and 90 mg CBD doses and with TurboCBD^{TM} technology

	45 mg	45 mg Turbo	90 mg	90 mg Turbo	Main Effect	Pairwise comparisons		
					p value	45–90	45–45T	90–90T
Total AUC (ng ml^{-1})	2252 ± 1301	2860 ± 1301	7115 ± 2978	10,865 ± 6322	< 0.001	0.012	1	0.088
Time to C_{max} (min)	113 ± 57	130 ± 56	123 ± 41	110 ± 41	0.742			
Total AUC to C_{max} (ng ml^{-1} kg^{-1})	5.2 ± 4.6	7.4 ± 5.9	15.3 ± 10.8	35.3 ± 31.7	< 0.001	0.957	1	0.039
C_{max} (ng ml^{-1})	16.8 ± 11.2	21.2 ± 9.7	54.6 ± 23.5	77.6 ± 40.6	< 0.001	0.003	1	0.161
$C_{BL\text{–}max}$ (ng ml^{-1} min^{-1})	0.2 ± 0.19	0.19 ± 0.11	0.56 ± 0.46	0.74 ± 0.34	< 0.001	0.032	1	1
$C_{max\text{–}6h}$ (ng ml^{-1} min^{-1})	− 0.06 ± 0.04	− 0.08 ± 0.04	− 0.2 ± 0.08	− 0.29 ± 0.18	< 0.001	0.016	1	0.238

Data presented as mean ± SD; $n = 12$. T, Turbo. One-way ANOVA with Bonferroni post hoc correction

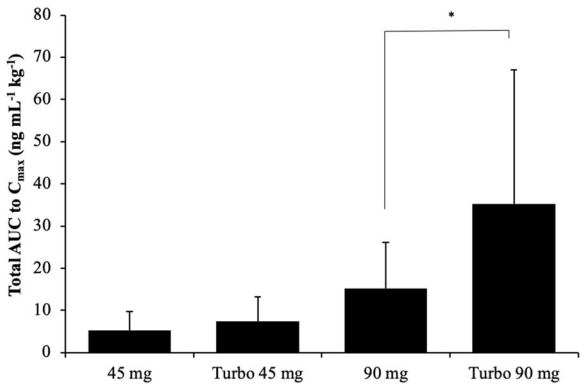

Fig. 2 Area under the curve (AUC) to peak plasma concentration (C_{max}), normalized to body weight, after consumption of generic 45 mg and 90 mg CBD doses, and with TurboCBD^{TM} technology. Mean ± SD $^{*}p < 0.05$

Cerebral Perfusion

There were no differences in MCA and PCA velocity (v) between baseline and C_{max} for either generic 90 mg or TurboCBD^{TM} 90 mg after controlling for E_TCO_2 (Table 3). When normalized to MAP, TurboCBD^{TM} 90 mg was associated with an increase in MCA conductance (c) at C_{max} (0.82 ± 0.21 cm s^{-1} mmHg^{-1}) compared with baseline (0.78 ± 0.22 cm s^{-1} mmHg^{-1}; $p < 0.001$; Fig. 3). In this subgroup ($n = 9$), MAP was decreased by 5% ($p = 0.016$) with TurboCBD^{TM} 90 mg, whereas MAP was unchanged with the generic 90 mg dose. Time-synced placebo showed no differences in MAP or in MCA/PCA velocity and conductance. Inter-baseline day-day variabilities (coefficient of variance) for MCAv and PCAv were 8.7% and 12.3%, respectively.

Haematological

Inflammation

CRP and sedimentation were unchanged by CBD dose (Table 4). Delta CRP was also unaffected across 5 h with different CBD doses (Fig. 4).

Metabolic

Insulin and glucose were unchanged by CBD dose until 3 h (Table 4). At 5 h (i.e., 1 h post-snack), the delta insulin and glucose levels were increased, yet indifferently between CBD doses (+ 75% and + 23% for insulin and glucose, respectively).

Complete Blood Count

Aside from suspected fluctuations in plasma volume diuresis occurring over 6 h of rest, there were no interaction effects between CBD dose and time (Table 4).

Table 2 Blood pressure at baseline and peak CBD concentration (C_{max}) with generic 90 mg CBD and TurboCBD^{TM} 90 mg doses

		Baseline	At C_{max}	p value
Generic 90 mg	Systolic BP (mmHg)	120 ± 5	120 ± 4	0.579
	Diastolic BP (mmHg)	65 ± 9	65 ± 8	0.684
	MAP (mmHg)	84 ± 7	83 ± 6	0.625
	Heart rate (bpm)	68 ± 17	67 ± 17	0.671
TurboCBD^{TM} 90 mg	Systolic BP (mmHg)	121 ± 10	121 ± 8	0.515
	Diastolic BP (mmHg)	65 ± 6	62 ± 7	0.092
	MAP (mmHg)	84 ± 6	81 ± 6	0.098
	Heart rate (bpm)	67 ± 19	66 ± 19	0.613

Data presented as mean ± SD; $n = 12$. BP, blood pressure; MAP, mean arterial pressure. Mean paired t test

Table 3 Middle- and posterior cerebral artery velocity and conductance at baseline and C_{max}

		Baseline	At C_{max}	p value
Generic 90 mg	MCAv (cm s^{-1})	67 ± 18	65 ± 15	0.71
	PCAv (cm s^{-1})	44 ± 6	45 ± 8	0.141
	MAP ($mmHg^{-1}$)	84 ± 8	82 ± 6	0.27
	MCAc (cm s^{-1} $mmHg^{-1}$)	0.81 ± 0.2	0.81 ± 0.18	0.963
	PCAc (cm s^{-1} $mmHg^{-1}$)	0.53 ± 0.09	0.55 ± 0.09	0.321
TurboCBD^{TM} 90 mg	MCAv (cm s^{-1})	66 ± 23	68 ± 21	0.174
	PCAv (cm s^{-1})	48 ± 12	49 ± 9	0.289
	MAP ($mmHg^{-1}$)	85 ± 5	81 ± 6*	0.016
	MCAc (cm s^{-1} $mmHg^{-1}$)	0.78 ± 0.22	0.84 ± 0.23***	< 0.001
	PCAc (cm s^{-1} $mmHg^{-1}$)	0.57 ± 0.11	0.61 ± 0.09	0.153

Data presented as mean ± SD; n = 9. Cerebral blood velocity (v) and conductance (c) normalized to end-tidal CO_2. MCA, Middle cerebral artery; PCA, posterior cerebral artery. Paired t test. *$p < 0.05$, ***$p < 0.001$

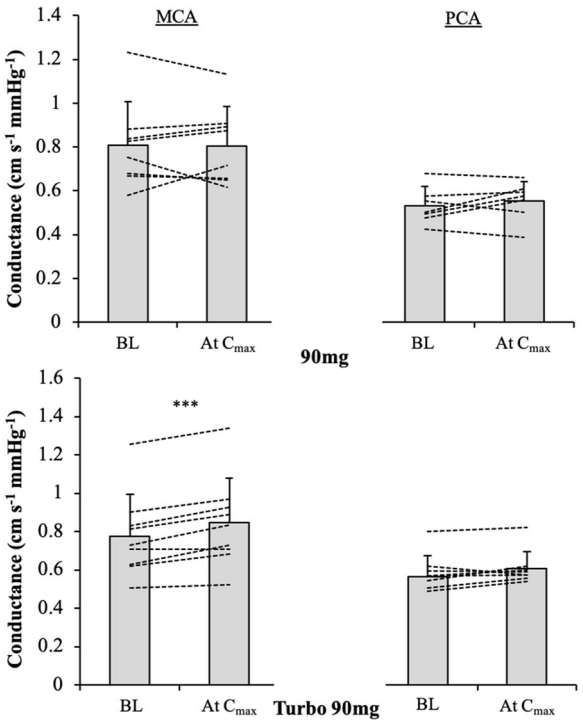

Fig. 3 Conductance of middle cerebral artery (MCA; left panels) and posterior cerebral artery (PCA; right panels) at baseline (BL) and at peak plasma concentration (C_{max}) with the generic 90 mg (top) and TurboCBD^{TM} 90 mg (bottom) doses. Individual (dashed lines) and mean ± SD (bars) are shown. ***$p < 0.001$

CBD Excreted in Urine

CBD excreted in the urine was not different between doses or at each time point post-consumption (Fig. 5). All doses, except TurboCBD^{TM} 45 mg (p = 0.673), were different compared with placebo (p = 0.036, p = 0.002 and $p < 0.001$ for generic 45 mg, generic 90 mg and TurboCBD^{TM} 90 mg doses, respectively). Quantity of CBD excreted in urine was not correlated with C_{max}, $C_{BL\text{-}max}$, $C_{max\text{–}6h}$ or plasma CBD at 180 and 360 min.

DISCUSSION

This study was the first to investigate a joint pharmacokinetic-physiological time course of multiple recreational-equivalent (< 100 mg) dosages of CBD in healthy adult humans. There was an apparent dose relationship between the generic 45 mg vs. 90 mg CBD doses (+ 225% change in peak plasma CBD, respectively). The incorporation of TurboCBD^{TM} improved CBD bioavailability by 111% compared with an equivalent generic 90 mg dose. These differences in TurboCBD^{TM} and the generic 90 mg doses were statistically different at both 90 (+

Table 4 Haematological measures at baseline and following ingestion of generic 45 mg or 90 mg CBD doses and with TurboCBD™

	Time	Placebo	45 mg	Turbo 45 mg	90 mg	Turbo 90 mg	By group	*p* value
Sedimentation (mm 3.6 ks^{-1})	Baseline	4.8 ± 5	4.3 ± 4	5.3 ± 5.1	4.4 ± 3.6	4.5 ± 4	Dose	0.898
	1.5 h	4.8 ± 4.3	4.7 ± 3.6	5.1 ± 5.6	4.8 ± 3.6	5.5 ± 5.2	Time	0.892
	3 h	4.8 ± 4.1	4.9 ± 4.2	4.8 ± 5	4.7 ± 3.4	5.4 ± 4.7	Interaction	1
	5 h	5 ± 4.4	5 ± 4.9	5.3 ± 4.8	4.6 ± 2.5	5.5 ± 6.1		
C-reactive protein (CRP; mg l^{-1})	Baseline	1.3 ± 1.7	1.8 ± 4.1	2.5 ± 5.5	1.1 ± 0.9	1.9 ± 3.2	Dose	0.593
	1.5 h	1.3 ± 1.7	1.8 ± 4	2.4 ± 5.2	1 ± 0.8	1.7 ± 2.8	Time	0.996
	3 h	1.4 ± 1.8	1.8 ± 4.1	2.4 ± 5.2	1 ± 0.8	1.7 ± 2.6	Interaction	1
	5 h	1.4 ± 1.8	1.7 ± 3.8	2.3 ± 5.1	1 ± 0.8	1.6 ± 2.5		
Glucose (mmol L^{-1})	Baseline	4.8 ± 5	4.3 ± 4	5.3 ± 5.1	4.4 ± 3.6	4.5 ± 4	Dose	0.829
	1.5 h	4.9 ± 0.2	4.8 ± 0.4	4.9 ± 0.4	4.8 ± 0.2	4.8 ± 0.2	Time	< 0.001
	3 h	4.9 ± 0.2	4.7 ± 0.4	4.8 ± 0.3	4.8 ± 0.2	4.7 ± 0.2	Interaction	0.967
	5 h	6.1 ± 0.9	5.9 ± 1	5.8 ± 0.9	5.8 ± 0.6	6 ± 0.7		
Insulin (pmol L^{-1})	Baseline	86.7 ± 49.7	86.7 ± 54.9	83.7 ± 50.3	77.7 ± 83.5	80.8 ± 52.7	Dose	0.505
	1.5 h	50.4 ± 20.5	51.5 ± 21.3	53.9 ± 31.4	49.8 ± 20	53.2 ± 28	Time	< 0.001
	3 h	49.4 ± 19.1	40.6 ± 17.2	45.2 ± 22.2	42.3 ± 15.5	52.8 ± 33.1	Interaction	0.949
	5 h	151 ± 57.2	124.9 ± 77.8	134 ± 57.1	139.1 ± 87.4	174.8 ± 89.4		
White blood cell count (WBC; $\times 10^9$ L^{-1})	Baseline	6.4 ± 1.1	5.9 ± 1.1	6.2 ± 0.9	6.1 ± 1.4	6.5 ± 1.5	Dose	0.012
	1.5 h	6.5 ± 2.1	5.5 ± 0.9	5.9 ± 1.1	6.1 ± 1.2	6.2 ± 1.3	Time	0.636
	3 h	6.4 ± 1.8	5.7 ± 1.1	6 ± 1	5.9 ± 1.2	6.4 ± 1.5	Interaction	0.975
	5 h	6.4 ± 1.6	6 ± 1.3	5.9 ± 1.1	5.9 ± 1.2	6.2 ± 1.5		
Red blood cell count (RBC; $\times 10^{12}$ L^{-1})	Baseline	4.83 ± 0.32	4.9 ± 0.41	4.78 ± 0.3	4.79 ± 0.25	4.76 ± 0.21	Dose	0.137
	1.5 h	4.81 ± 0.33	4.8 ± 0.35	4.77 ± 0.31	4.74 ± 0.25	4.71 ± 0.24	Time	0.055
	3 h	4.88 ± 0.31	4.88 ± 0.32	4.88 ± 0.31	4.77 ± 0.31	4.81 ± 0.25	Interaction	0.986
	5 h	4.86 ± 0.28	4.88 ± 0.33	4.89 ± 0.32	4.77 ± 0.22	4.84 ± 0.26		
Haemoglobin (Hb; g/l)	Baseline	148 ± 8	149 ± 12	146 ± 6	146 ± 9	145 ± 5	Dose	0.077
	1.5 h	144 ± 8	144 ± 11	143 ± 7	143 ± 8	141 ± 6	Time	0.004
	3 h	146 ± 7	145 ± 9	146 ± 7	143 ± 9	143 ± 6	Interaction	0.992
	5 h	145 ± 8	146 ± 10	146 ± 8	142 ± 7	144 ± 6		
Haematocrit (Hct; %)	Baseline	43.6 ± 2.5	44.3 ± 3.7	43.1 ± 2.3	43.4 ± 2.5	43.1 ± 1.6	Dose	0.117
	1.5 h	43.4 ± 2.6	43.3 ± 3.2	43 ± 2.2	43 ± 2.1	42.6 ± 1.8	Time	0.051
	3 h	44.1 ± 2.4	44.2 ± 2.6	44 ± 2.1	43.1 ± 2.7	43.4 ± 2	Interaction	0.97
	5 h	44.1 ± 2.2	44.1 ± 2.7	44.2 ± 2.2	43.1 ± 2.1	43.7 ± 2		

Table 4 continued

	Time	Placebo	45 mg	Turbo 45 mg	90 mg	Turbo 90 mg	By group	*p* value
Mean corpuscular volume (MCV; fl)	Baseline	90.4 ± 2.9	90.5 ± 3	91.1 ± 3.9	90.6 ± 3.2	90.5 ± 2.8	Dose	0.916
	1.5 h	90.4 ± 3.5	90.4 ± 3.3	90.3 ± 3	90.7 ± 2.8	90.5 ± 3	Time	0.75
	3 h	90.4 ± 2.9	90.6 ± 3	90.4 ± 3.1	90.3 ± 3	90.3 ± 2.9	Interaction	0.859
	5 h	90.7 ± 3.3	90.5 ± 3.2	90.5 ± 3	90.5 ± 3	90.4 ± 2.8		
Mean corpuscular haemoglobin (MCH; pg)	Baseline	30.6 ± 1.1	30.5 ± 1.3	30.6 ± 1.3	30.5 ± 1.4	30.5 ± 1.2	Dose	0.281
	1.5 h	30 ± 1.3	30 ± 1.3	30.1 ± 1.3	30.1 ± 1.4	30 ± 1.2	Time	< 0.001
	3 h	29.9 ± 1.3	29.9 ± 1.1	30 ± 1.3	29.9 ± 1.4	29.8 ± 1.2	Interaction	0.995
	5 h	29.8 ± 1.2	29.8 ± 1.2	29.9 ± 1.2	29.9 ± 1.3	29.7 ± 1.2		
Mean corpuscular haemoglobin concentration (MCHC; g l^{-1})	Baseline	339 ± 5	336 ± 5	339 ± 5	337 ± 5	337 ± 5	Dose	0.103
	1.5 h	332 ± 4	332 ± 4	333 ± 4	332 ± 5	331 ± 5	Time	< 0.001
	3 h	330 ± 4	329 ± 4	331 ± 4	331 ± 5	330 ± 5	Interaction	0.902
	5 h	329 ± 3	330 ± 3	330 ± 5	330 ± 5	329 ± 5		
Platelets (Plt; $\times 10^9$ L^{-1})	Baseline	203 ± 33	199 ± 35	199 ± 37	200 ± 48	201 ± 44	Dose	0.714
	1.5 h	197 ± 45	197 ± 37	201 ± 39	197 ± 46	197 ± 41	Time	0.51
	3 h	206 ± 41	200 ± 31	201 ± 36	204 ± 44	203 ± 44	Interaction	0.998
	5 h	207 ± 43	199 ± 37	202 ± 43	196 ± 43	205 ± 42		

Data presented as mean ± SD; n = 12. Linear mixed model with Bonferroni correction

86%) and 120 min (+ 65%; Fig. 1). Moreover, only the TurboCBD™ 90 mg dose was elevated greater than placebo at 30 min (p = 0.017) and

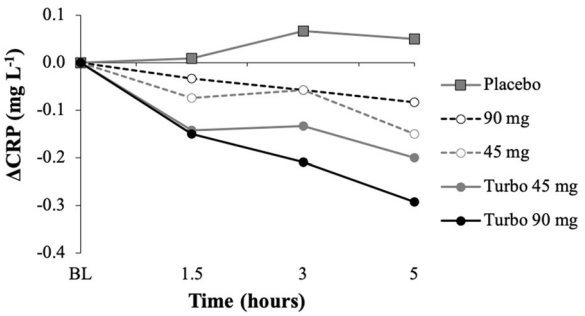

Fig. 4 Delta (Δ) C-reactive protein (CRP) normalized to baseline and at 1.5, 3 and 5 h post-ingestion of placebo (double solid), TurboCBD™ 45 mg (grey solid), generic 45 mg CBD (grey dashed), TurboCBD™ 90 mg (black solid) and generic 90 mg CBD (black dashed). SD not included for clarity (n = 12)

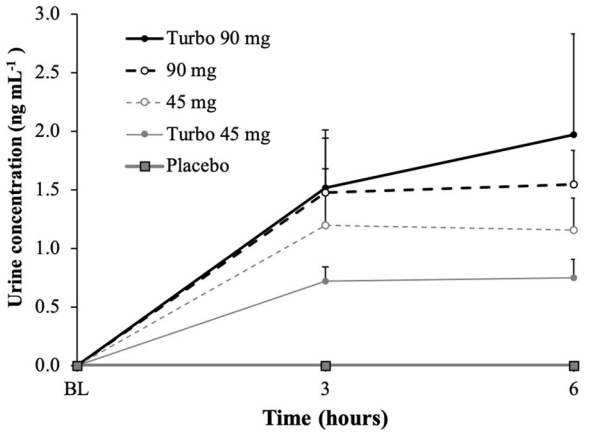

Fig. 5 Cannabidiol (CBD) concentration in urine at baseline (BL), 3 and 6 h following consumption of placebo (solid grey solid squares), 45 mg (dashed grey open circles) and 90 mg (dashed black open circles) doses of CBD with TurboCBD™ (solid black solid circles) and without (solid grey solid circles). Standard error included for clarity

remained elevated at 4 h (p = 0.002). Consistent with higher CBD availability, TurboCBD^{TM} 90 mg and the peak plasma concentration were associated with an increase in MCA conductance and slight reduction in blood pressure compared with baseline and the 90 mg control. In contrast, there were no differences in any pharmacokinetic-physiological parameters at 45 mg. The following discussion considers the evidence, experimental limitations and relevance underlying the findings of this study.

Pharmacokinetics and Comparison with Previous Studies

In a recent study, gelatine matrix pellets were superior to an oromucosal spray in improving CBD bioavailability at recreational (100 mg) dosing [13]. Optimization of CBD absorption has obvious benefits for general health and recreational usage. In the current study, TurboCBD^{TM} formulation enhanced the uptake and total absorption of CBD compared with an equivalent generic CBD capsule (Fig. 2), also exhibiting a potential advantage over gelatine matrix pellets (Fig. 6) [13]. Specifically, in this latter study, time to C_{max} occurred within 3-3.5 h, whereas in the current study it occurred within 120 min. The mechanisms by which the TurboCBD^{TM} formulation may accelerate CBD bioavailability is unclear; however, the process is speculated to be related to the presence by which long chain fatty acids high in oleic acid are associated through the dehydration processing technique with the CBD, leading to improved uptake of the CBD allowing for higher volumes of CBD to enter the circulatory system, perhaps more expediently by bypassing first-pass liver metabolism. One putative mechanism of this latter pathway is that the fatty acids mediate the bypassing of first-pass liver metabolism in the short term, resulting in lower initial levels of metabolites [19]. A novel, albeit preliminary, exploration of changes in liver metabolites (e.g., 6a-OH-CBD, 7-OH-CBD, 7-CBD-COOH; iC42, Colorado, USA [20]) was conducted in a sub-group of the current study following the 90 mg TurboCBD^{TM} and generic 90 mg control group (n = 5 and 4, respectively; Fig. 7). Albeit under-powered and thus not significant, the apparent close trend of lower metabolite levels (i.e., 7-OH-CBD and 7-CBD-COOH) with TurboCBD^{TM} 90 mg compared with the generic 90 mg is promising, as it is in line with first-pass liver metabolism circumvention. Post-hoc statistical power calculations based on the C_{max} data from Fig. 7 indicate a required sample size of n = 10–17 for 7-OH-CBD and 7-CBD-COOH, respectively.

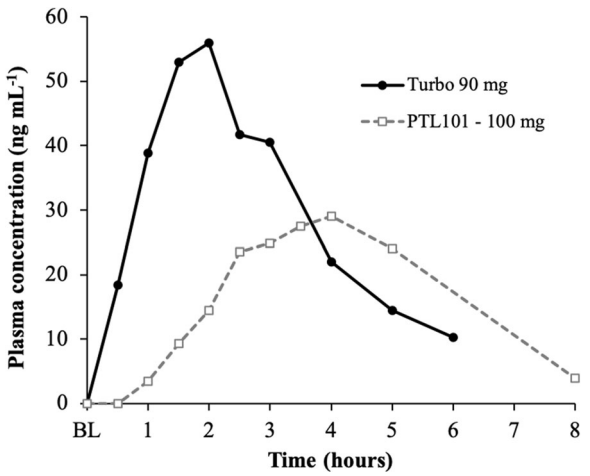

Fig. 6 Pharmacokinetic comparison of the ingestion of TurboCBD^{TM} 90 mg (solid black solid circles) and PTL101-100 mg (dashed grey open squares). Only mean data are shown for clarity. PTL101-100 mg data via gelatin matrix pellets, modified from Atsmon and colleagues [12]

Physiological Changes

In select animal models (i.e., ischaemic stroke in mice and piglets), CBD appears to have cerebral neuroprotective effects via CB_1 and CB_2-independent mechanisms [21] associated with increases in cerebral blood flow [22]. In healthy humans, regional cerebral blood flow was first evaluated using ^{99m}Tc-ECD SPECT (technetium-99m labelled ethyl-cisteinate-dimer labelled-single-photon emission computed tomography; [23]), which identified region-specific increases (i.e., the medial temporal cortex) in cerebral metabolism with 400 mg CBD compared with placebo. Both MCA and PCA supply the temporal lobe [24], but the parahippocampal gyrus,

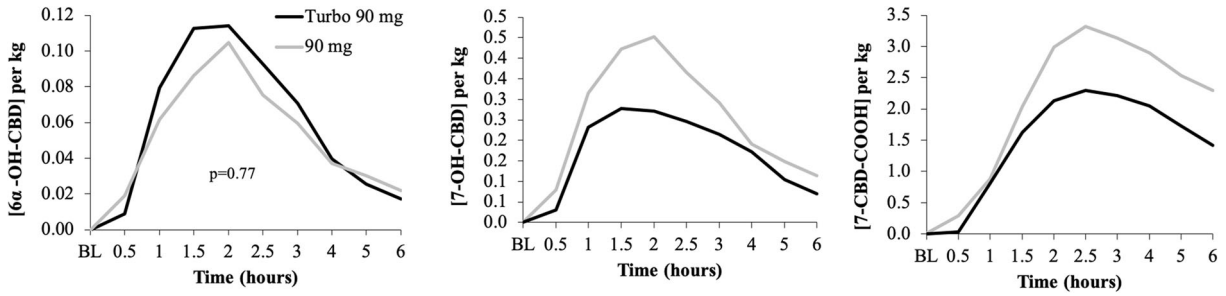

Fig. 7 Liver metabolites (left to right, 6α-OH-CBD, 7-OH-CBD and 7-CBD-COOH) following TurboCBD™ 90 mg or generic 90 mg doses. Linear mixed model with Bonferroni correction

the region encompassing the medial temporal cortex, appears to predominantly receive blood flow from the MCA [24]. This is interesting because if CBD induces region-specific changes in brain regions downstream from the MCA (e.g., parahippocampal gyrus), it presumably alters pial vasomotor tone and thus oxygen demand. Therefore, it is perhaps not surprising that coinciding upstream MCA conductance was increased with TurboCBD™, as an increased MCA conductance would align with a blood pressure-mediated increase in metabolic demand. The current study did not observe changes with the generic CBD dose, suggestive of an uptake-dependent threshold, which was shown to be elevated with TurboCBD™ compared with the generic dose.

Given only working memory in healthy adults was evaluated (and was unaltered), it is unclear from the current study whether there are neuropsychological implications of increased CBD bioavailability in healthy young volunteers. ^{99m}Tc-ECD SPECT [8] and functional magnetic resonance imaging (fMRI) [9] have shown an improvement in visual analogue mood scale scores following CBD in patients with social anxiety disorder. Interestingly, these patients also exhibit region-specific differences in regional cerebral blood flow patterns (e.g., a decrease in parahippocampal gyrus activity) compared with otherwise healthy individuals, which may be related to the anxiolytic effects of CBD [8]. Additionally, it seems likely that such changes in neuropsychological effects following CBD may also occur in older individuals who exhibit reduced cerebral vascular conductance [25] or in patients with cerebrovascular dysfunction [26]. Acute and chronic dosing of CBD in these more at-risk populations warrant further investigation.

Our finding of an augmented middle cerebral artery conductance (as an index of cerebral perfusion), driven more so by a slight reduction in blood pressure rather than an increase in velocity, at C_{max} is noteworthy. Administration of CBD has previously been shown to induce endothelium- and nitric oxide-dependent vasorelaxation in human mesenteric arteries [27]. A recent systematic review of five healthy human studies of acute (e.g., single dose ranging from 100 to 1200 mg) and chronic (e.g., single daily dose for 20–42 days) CBD intake unanimously reported blood pressure and heart rate are unaffected during at least control (i.e., resting and unstressed) conditions [22]. However, a study published in the same year showed a reduction in resting systolic blood pressure following 600 mg compared with placebo [28]. It is therefore very likely that the increases in CBD bioavailability of TurboCBD™ play a major role in our blood pressure findings; however, it is also relevant to consider the added influence of the combined ginkgo biloba, ginseng and hemp oil. Individually, the literature is controversial; however, at least in healthy young individuals, the consensus appears to be a null effect. For example, repetitive days of ginkgo biloba [29] or American ginseng [30] supplementation does not appear to affect cognitive function or blood pressure. Finally, hemp seed oil, although in both TurboCBD™ and generic CBD capsules, has also shown mixed results, with effects (if any) being observed after weekly dosing (reviewed in: [31]).

Future studies are clearly warranted to investigate the interactions of CBD on the mechanisms of blood pressure regulation.

Haematological Responses

CB_1 and CB_2 are widely, yet conservatively, distributed throughout the central nervous system (i.e., most densely in the basal ganglia, hippocampus and cerebellum [7]) and peripheral immune system tissues (notably the tonsils, spleen, mononuclear cells and thymus; [32]). Additionally, specific classes of CBD may actually act allosterically as non-competitive agonists on CB receptors [33]. Amongst many other functions, CBD has been reported to have immunomodulatory [34, 35] and anti-inflammatory actions [36, 37]. Despite these reports, although some trends were evident, we observed no significant changes in any of our commonly used clinical metrics of immunomodulation and inflammation (Fig. 4; Table 4). Although some of these measures lack precision concerning the mechanism of cellular immunomodulation and inflammation, it should be noted that our healthy volunteers were unlikely to be in a pro-inflammatory state. Perhaps biomarkers with greater sensitivity and specificity to specific inflammatory states (e.g., ischaemic reperfusion, diabetes, oxidative damage, inflammatory apoptosis), which have been more typically shown to be improved with CBD ingestion [27, 38], may be better suited to shed light on potential anti-inflammatory properties of CBD and deserve further study (see: "Experimental Limitations" below).

Experimental Considerations

A few experimental considerations regarding the present study deserve mention. First, as our exploratory sample size was only conducted in males, we were unable to address possible sex-related differences in CBD usage or extend our findings to more at-risk populations and conditions that might exhibit a differential response to CBD administration; as such we cannot, and should not, automatically assume similar pharmacokinetics and physiological phenotypes in these different populations. Even though our young healthy participants had no adverse issues with the tolerability of any of the dosing interventions, if this technology is to be applied to different populations, further investigation into the interactions with other medications (e.g., reliant upon normal cytochrome P450 function [39]) and potential risks—allergic, metabolic or otherwise—is an important step that should be ensured. Finally, although there are well-established laboratory reference standards for the main plasma CBD assays, these are not currently available for the liver metabolites. Therefore, these liver metabolite data are not quantitative and are based on relative peaks and extrapolation of the 11-OH-CBD curves to estimate these hydroxyl-CBD compounds. As such, these metabolites are exploratory in nature and should be interpreted with caution.

CONCLUSION

Using a new oral delivery method (TurboCBD^{TM}), circulating CBD was enhanced compared with equivalent generic CBD capsules. This greater CBD absorption was associated with the highest, albeit recreational, dose (90 mg), and there was a tendency for mean arterial pressure to be reduced, which drove elevations in cerebral perfusion. As the current study was well tolerated by healthy young males, further acute and chronic dosing investigations in older and cerebrovascular-compromised patients may shed light on the vascular and clinical impacts of increased CBD bioavailability.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Philip N Ainslie acts as a Scientific Advisor for Lexaria Bioscience Corp. Alexander Patrician, Maja Versic-Bratincevic, Tanja Mijackia, Ivana Banic, Mario Marendic, Davorka Sutlović and Željko Dujić declare they have no conflict of interest.

Compliance with Ethics Guidelines. All procedures were performed in accordance with the Ethics Committee at the University of Split School of Medicine and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written informed consent prior to completion of any data collection.

Data Availability. The datasets generated and/or analyzed during the current study are not yet publicly available, but are available upon request.

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