Supplementary Material

1 Supplementary Data

1.1 Preparation of urine samples for cannabinoid analysis

Cannabinoids were extracted from 5 mL urine by liquid/liquid extraction after addition of 50 µL of the internal standard mix (D3-CBD, D3-THC, D3-OH-THC, D3-COOH-THC, each at 1 µg/mL in methanol) and after hydrolysis of the phase-II metabolites. For the hydrolysis, samples were adjusted to pH 7 with 1 mL of 0.8 M phosphate buffer and then incubated after addition of 50 µL β-glucuronidase from *E. coli* at 50 °C for 1 h. Six mL of n-pentane were added and the mixture was shaken for 20 min and subsequently centrifuged at 600 g for 5 min. The n-pentane layer was separated and evaporated to dryness under reduced pressure. The dry residue was derivatized with 80 µL MSTFA/NH4I/ethanethiol 1000:2:3 (v:w:v) for 30 min at 80 °C and 6 µL were injected onto the gas chromatograph/mass spectrometry instrument.

1.2 Preparation of serum samples for cannabinoid analysis

Cannabinoids were extracted from 2 mL serum by liquid/liquid extraction after addition of 20 µL of the internal standard mix (D3-CBD, D3-THC, D3-OH-THC, D9-COOH-THC, each at 1 µg/mL in methanol). The mixture was adjusted to pH 5.2 with 100 µL of 4 M sodium acetate buffer. Five mL of a 50:50 (v:v) mixture of n-pentane and tert-butyl-methyl-ether were added and the mixture was shaken for 20 min and subsequently centrifuged at 600 g for 5 min. The organic layer was separated and evaporated to dryness under reduced pressure. The dry residue was derivatized with 80 µL MSTFA/NH4I/ethanethiol 1000:2:3 (v:w:v) for 30 min at 80 °C and 6 µL were injected onto the gas chromatograph/mass spectrometry instrument.

1.3 Gas chromatography/tandem mass spectrometry (GC/MS/MS)

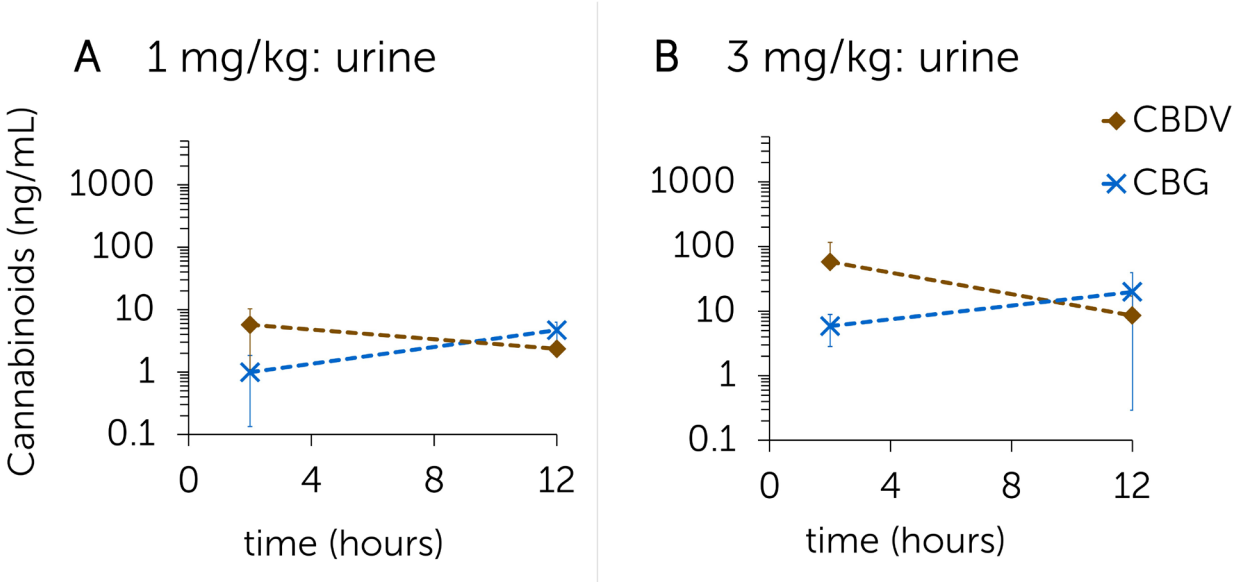
Analyses were performed using a Thermo Scientific TSQ 8000EVO tandem mass spectrometer coupled to a Thermo Scientific Trace 1310 gas chromatograph. A J&W Ultra 1 column (length 17 m, I.D. 0.2 mm, film thickness 0.11 µm) was employed, and helium was used as carrier gas at a constant pressure of 17.6 psi. An aliquot of 6 µL of the sample extract was injected into the GC/MS/MS system, which was operated in split mode (1:10). The GC temperature was ramped as follows: initial temperature = 157 °C, program rate = 20 °C/min to 325 °C, constant temperature = 325 °C for 1 min. The injection port and transfer line were heated to 300 °C. The trimethylsilylated analytes were measured using selected reaction monitoring (SRM) after electron ionisation (EI) and collision induced dissociation (CID) with argon as collision gas. The diagnostic ion transitions (listed as m/z), retention times (RT) and collision energies (CE) for each compound are presented in Table 1S.

Table 1S: Diagnostic ion transitions (specified as m/z), retention times (RT in min) and collision energies (CE in V) for each analyte and the corresponding internal standards (ISTD).

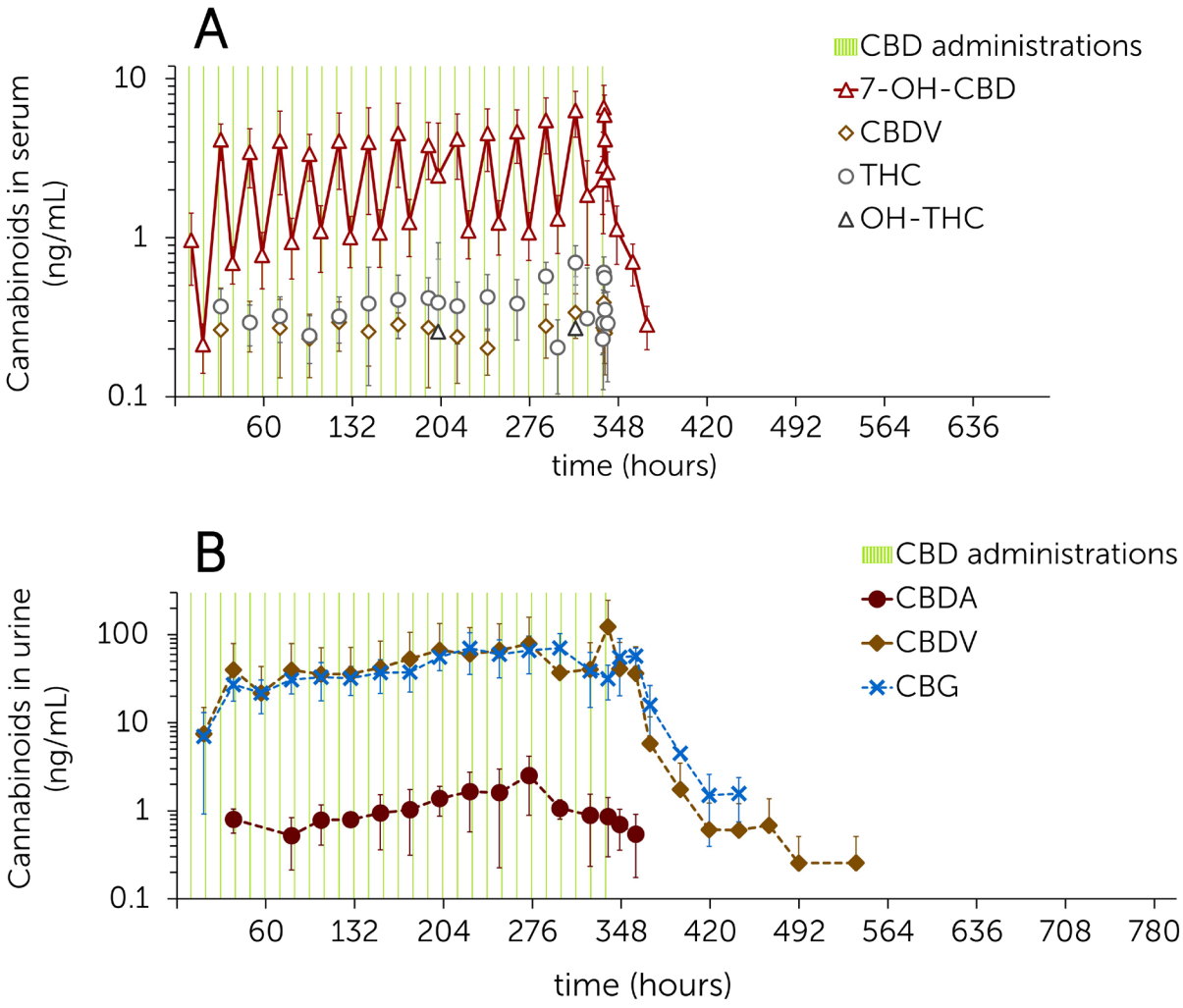
Cannabinoid	**RT**	**m/z**	**(CE)**	**ISTD**	**RT**	**m/z (CE)**	
CBD	4.33	390/301	(8)	D3-CBD	4.32	393/304	(10)
CBDA	5.45	491/133	(29)	D9-Carboxy-THC	6.28	380/314	(10)
CBDV	3.63	362/273	(7)	D3-Hydroxy-THC	5.78	374/292	(13)
CBG	5.03	337/321	(9)	D3-CBD	4.32	393/304	(10)
7-COOH-CBD	5.70	443/119	(14)	D9-Carboxy-THC	6.28	380/314	(10)
7-OH-CBD	5.36	443/337	(9)	D3-Hydroxy-THC	5.78	374/292	(13)
COOH-THC	6.30	371/305	(12)	D9-Carboxy-THC	6.28	380/314	(10)
OH-THC	5.79	371/305	(7)	D3-Hydroxy-THC	5.78	374/292	(13)
THC	4.72	389/371	(11)	D3-THC	4.71	389/374	(10)

Abbreviations: CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol; 7-COOH-CBD, 7-carboxy-cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; THC, Δ9-tetrahydrocannabinol; COOH-THC, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol; OH-THC, 11-hydroxy-Δ9-tetrahydrocannabinol.

2 Supplementary Figures



Supplementary Figure 1S: Mean ± standard deviation of cannabidivarin (CBD) and cannabigerol (CBG) in urine after single oral administration of CBD paste in two different doses (1mg/kg po (A); 3mg/kg po (B)).



Supplementary Figure 2S: Mean ± standard deviation of the following cannabinoid concentrations: 7-hydroxy-cannabidiol (7-OH-CBD), cannabidivarin (CBDV), Δ9-tetrahydrocannabinol (THC) and 11-hydroxy-THC (OH-THC) in serum (A), and cannabidiolic acid (CBDA), CBDV and cannabigerol (CBG) in urine (B) following multiple administrations of CBD paste (3 mg/kg po) twice daily over two weeks with subsequent sample collection.