Pharmacokinetics of different cannabidiol oil formulations in Sprague Dawley rats

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PURPOSE

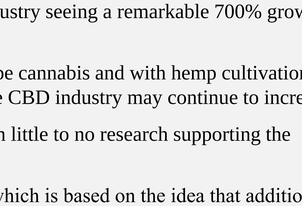
- Use of cannabidiol (CBD) containing products for a number of indications is rapidly increasing with the United States CBD industry seeing a remarkable 700% growth in the fiscal year 2019[1].
- CBD is the major cannabinoid in hemp-type cannabis and with hemp cultivation being made legal in 2018 the growth of the CBD industry may continue to increase[2].
- Claims made regarding CBD products with little to no research supporting the information infiltrate the industry.
- The "entourage effect" is one such claim which is based on the idea that additional compounds found in products derived from whole plant extracts makes these products more effective.
- Products from whole plant extracts contain terpenes (linool, myrcene, limonene, etc), flavonoids (quercetin, cannflavin A and B, etc) and additional minor cannabinoids (cannabigerol, cannabidivarin, etc).

OBJECTIVE

- The major goal of this study is to determine if there is a difference in the major pharmacokinetic parameters between CBD oral formulations from isolate, broad spectrum (containing all terpenes, minor cannabinoids, flavonoids, but no Δ-9-tetrahydrocannabinol (Δ-9-THC)), and full spectrum (containing all terpenes, minor cannabinoids, flavonoids, and <0.3% Δ-9-THC).
- Determine if there is a difference in the pharmacokinetics between male and female Sprague Dawley rats.

METHODS

- Male and female *Sprague-Dawley* rats dosed 50 mg/kg (human equivalent dose of 8 mg/kg) and 150 mg/kg (human equivalent dose of 24 mg/kg)
- Blood samples drawn over 24 and/or 48 hours using BASi Culex automatic blood collection system.
- Plasma separated, subjected to protein precipitation and samples subjected to UPLC-MS/MS analysis.
- Instrument Conditions
  - Acquity BEH C18 column (2.1x100mm, 1.7µm)
  - Gradient elution of methanol : acetonitrile (50:50 v/v) and water with 0.1% formic acid using a flow rate of 0.35 mL/min over 5 minutes.



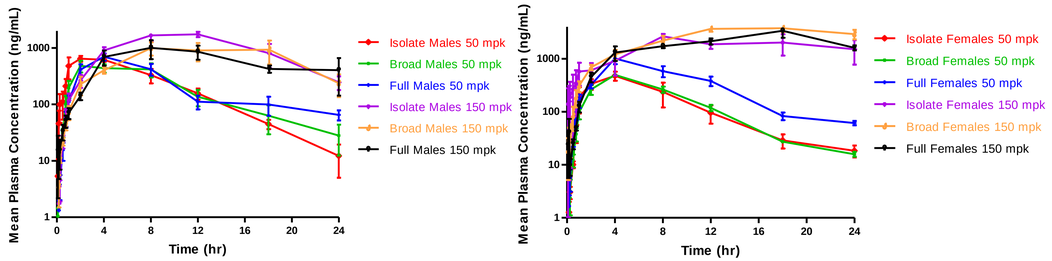


Figure 1. Mean plasma concentration time profiles. (N=4) after oral administration of CBD in males (left) and females (right)

WITHIN SEXES RESULTS

- For males there were no statistically significant differences seen in the major pharmacokinetic parameters between the formulations
- For females there was a difference seen in the maximum concentration, exposure, and absolute oral bioavailability for the full spectrum product at 50 mg/kg,
- Females saw an increase in maximum concentration and exposure for broad and isolate between the low and high doses.
- For both sexes there was a significant difference between the time to maximum concentration (T_{max}) between low and high doses.

Table 1. Pharmacokinetic parameters determined by noncompartmental analysis in males and females after oral administration of CBD. *indicates difference within formulations at same dose **indicates difference between high and low doses

Parameter	50 mg/kg Isolate Males	50 mg/kg Broad Males	50 mg/kg Full Males	150 mg/kg Isolate Males	150 mg/kg Broad Males	150 mg/kg Full Males	50 mg/kg Isolate Females	50 mg/kg Broad Females	50 mg/kg Full Females	150 mg/kg Isolate Females	150 mg/kg Broad Females	150 mg/kg Full Females
C_{max}/Dose (ug/L/mg/kg)	16 ± 1	12 ± 2	15 ± 3	13 ± 2	9 ± 2	9 ± 3	11 ± 3	10 ± 1	27 ± 11*	21 ± 2**	26 ± 3**	22 ± 6
T_{max} (h)	1 ± 0.3	4 ± 2	4 ± 0.0	12 ± 3**	13 ± 3**	9 ± 1**	4 ± 1	4 ± 0	5 ± 2	13 ± 3**	14 ± 2**	18 ± 0**
AUC_{inf}/Dose or AUC_{last}/Dose (ug*h/L/mg/kg)	101 ± 7	84 ± 11	136 ± 17	168 ± 28	117 ± 33	108 ± 24	72 ± 34	75 ± 9	203 ± 56*	273 ± 55**	422 ± 43**	316 ± 40
Bioavailability (%)	35 ± 2	25 ± 4	35 ± 6	-	-	-	25 ± 6	24 ± 2	57 ± 10*	-	-	-

BETWEEN SEXES RESULTS

- For the isolate and broad spectrum formulations no significant differences were seen between males and females
  - Males had 1.4x and 1.2x higher maximum concentration and 1.4x and 1.4x higher exposure for isolate and broad, respectively
- For the full spectrum formulation results were reversed.
  - Females had 1.5x the max concentration and 1.4x the exposure of males

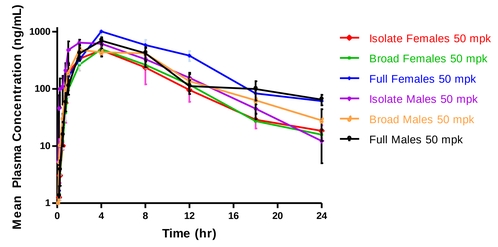


Figure 2. Males and females plasma concentration time profiles for 50 mg/kg dose

Table 2. Comparison of male versus females pharmacokinetic parameters for 50 mg/kg dose.

Parameter	CBD Isolate Males	CBD Isolate Females		CBD Broad Males	CBD Broad Females		CBD Full Males	CBD Full Females
T_{max} (hr)	3 ± 2	4 ± 1		5 ± 2	4 ± 0		4 ± 0	6 ± 2
C_{max} (ng/mL)	739 ± 59	542 ± 67		617 ± 58.7	498 ± 21		699 ± 104	1030 ± 208
AUC (hr*ng/mL)	5078 ± 328	3603 ± 967		5132 ± 1157	3744 ± 226		6805 ± 868	9271 ± 1614
CL (L/hr/kg)	10 ± 1	16 ± 3		11 ± 2	14 ± 1		8 ± 1	6 ± 1
V_d (L/kg)	48 ± 7	115 ± 36		70 ± 9	82 ± 5		79 ± 26	42 ± 13*
F (%)	35.0 ± 2.3	24.9 ± 6.0		35.4 ± 8.0	23.9 ± 1.8		47 ± 6	57 ± 10

CONCLUSIONS

- The full spectrum product had a higher absolute oral bioavailability in both male and female rats.
  - Supports the claim that the product derived from the whole plant with no post-processing is more well absorbed.
  - Changes in absorption may be due to other compounds present in the full spectrum product (i.e. terpenes have been shown to increase bioavailability of other compounds[3])
  - This may not be seen for the broad spectrum formulation as it must go through an extraction process to remove the Δ-9-THC, exposing the product to heat and possibly removing the volatile compounds.
- Formulations must be analyzed for volatile compound content to confirm what additional analytes are present in each.
- Dose of Δ-9-THC in full spectrum product calculated to be 0.2 mg/kg. Further studies delivering this dose with 50 mg/kg CBD and no other compounds will be performed to confirm if Δ-9-THC causes changes in maximum concentration and exposure.
- Data from this study will be used to develop *in silico* models to predict the behavior of CBD in other species
- Additional studies of CBD interaction with other natural products, kratom and kava, are underway.

REFERENCES

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2. 115th Congress of the United States (2017-2018). S.3042 Agricultural Improvement Act of 2018.
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ACKNOWLEDGMENTS

This work was performed with support from the University of Florida Clinical and Translation Science Institute's Translational Drug Development Core and is part of the University of Florida's "Creating the Healthiest Generation" Moonshot Initiative, which is supported by the UF Office of the Provost, UF Office of Research, UF Health, UF College of Medicine, and the UF Clinical and Translational Science Institute