CBD/CBDA rich hemp: Pharmacokinetics across species and quality control for practitioners to consider

Presented by

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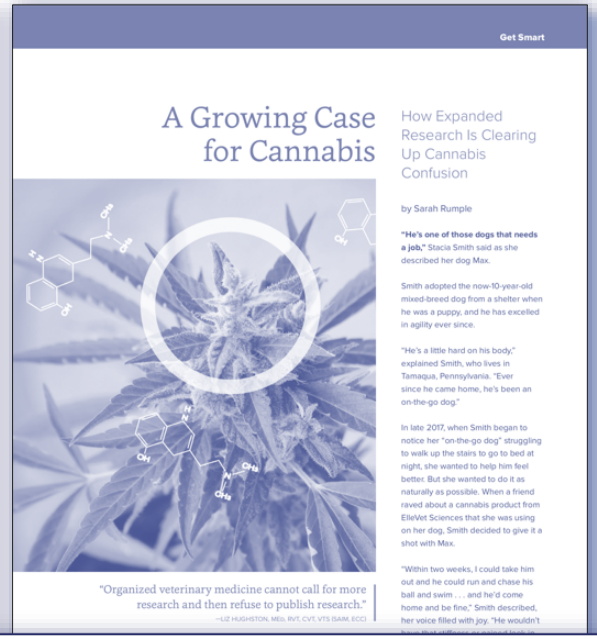
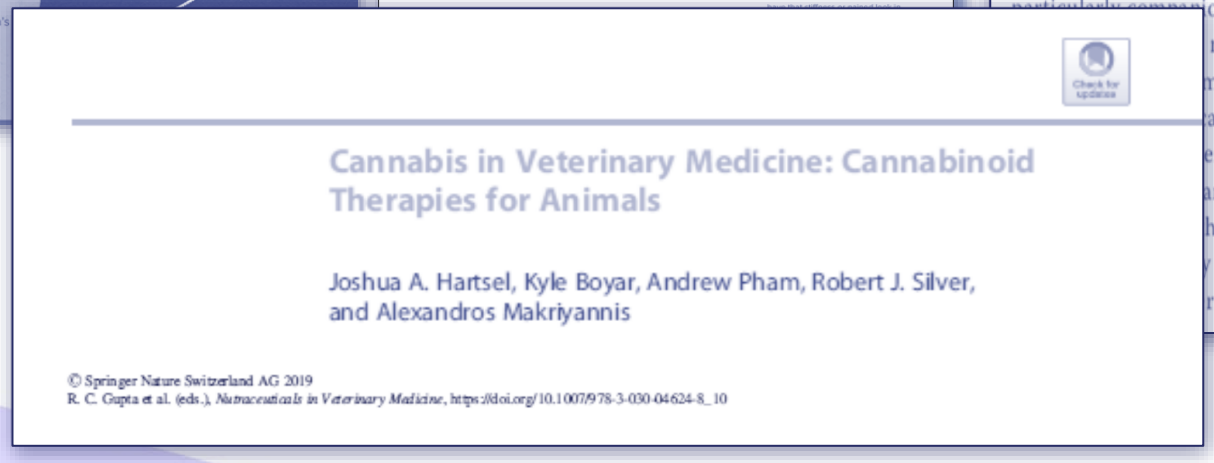
ElleVet Sciences Chief Medical Officer
Professor at Cornell University College of Veterinary Medicine

#Trending





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Endocannabinoid system (ECS)

- Unless you're a protozoa or an insect, you have an ECS!
- Phylogenetically developed concurrently with the nervous system

Who learned about the ECS in school?
How often are you asked about CBD?

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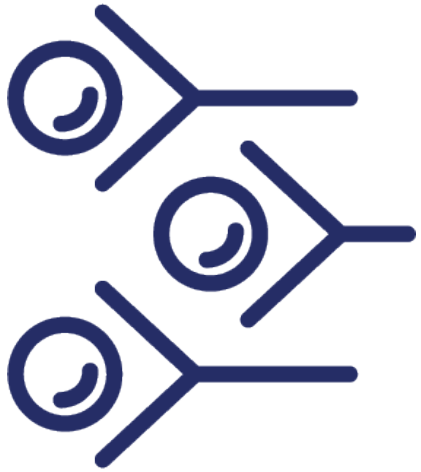
Endocannabinoid system (ECS)

- Largely eluded scientists until mid-1990s
- Legal and regulatory issues surrounding cannabis and associated molecules
- 2018 Farm Bill → explosion of interest, products, and research



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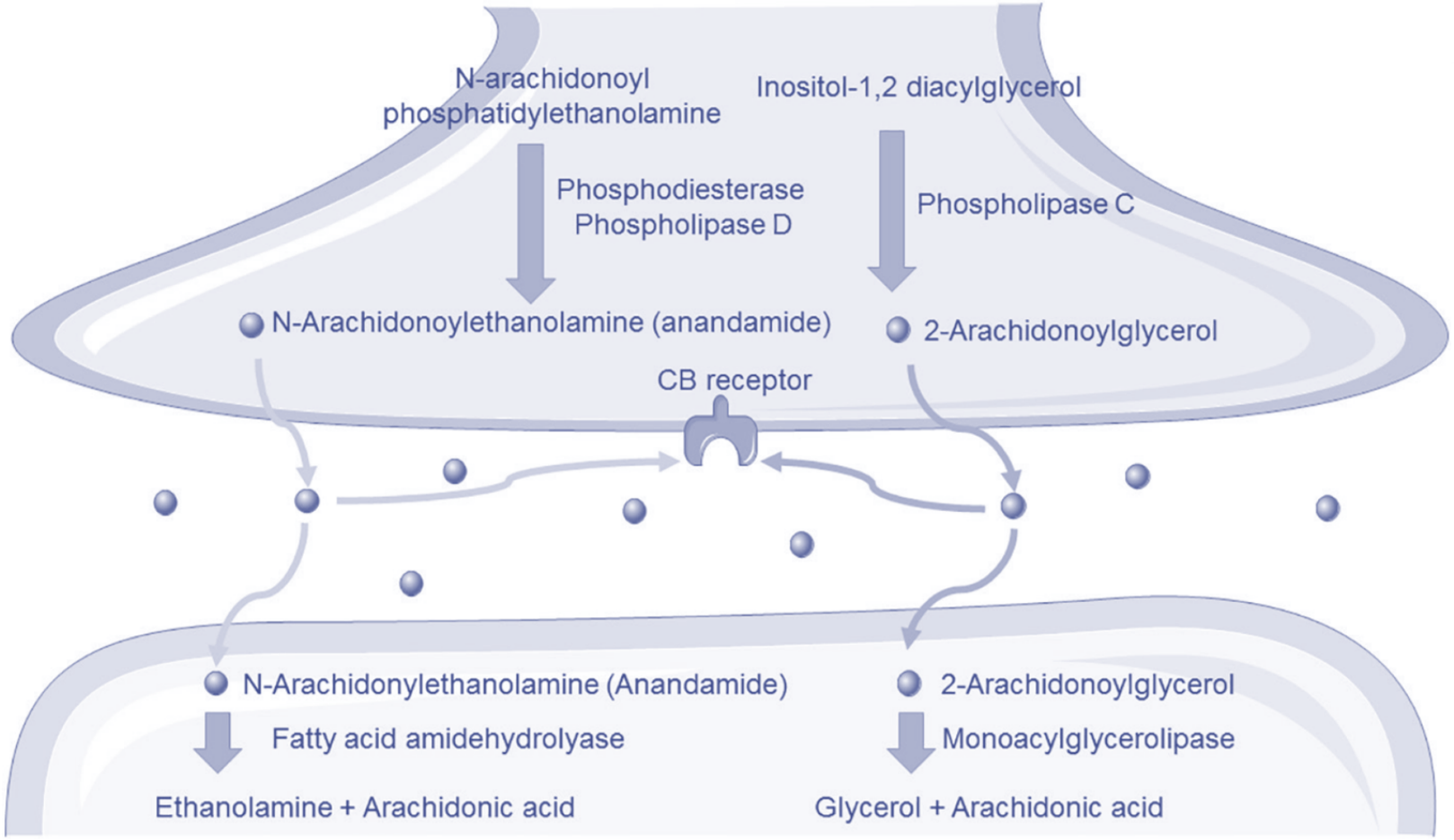
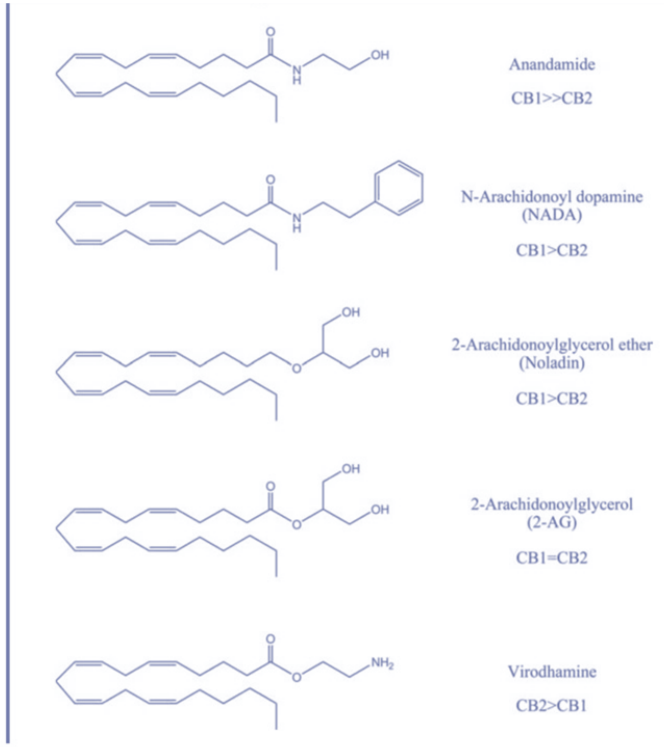
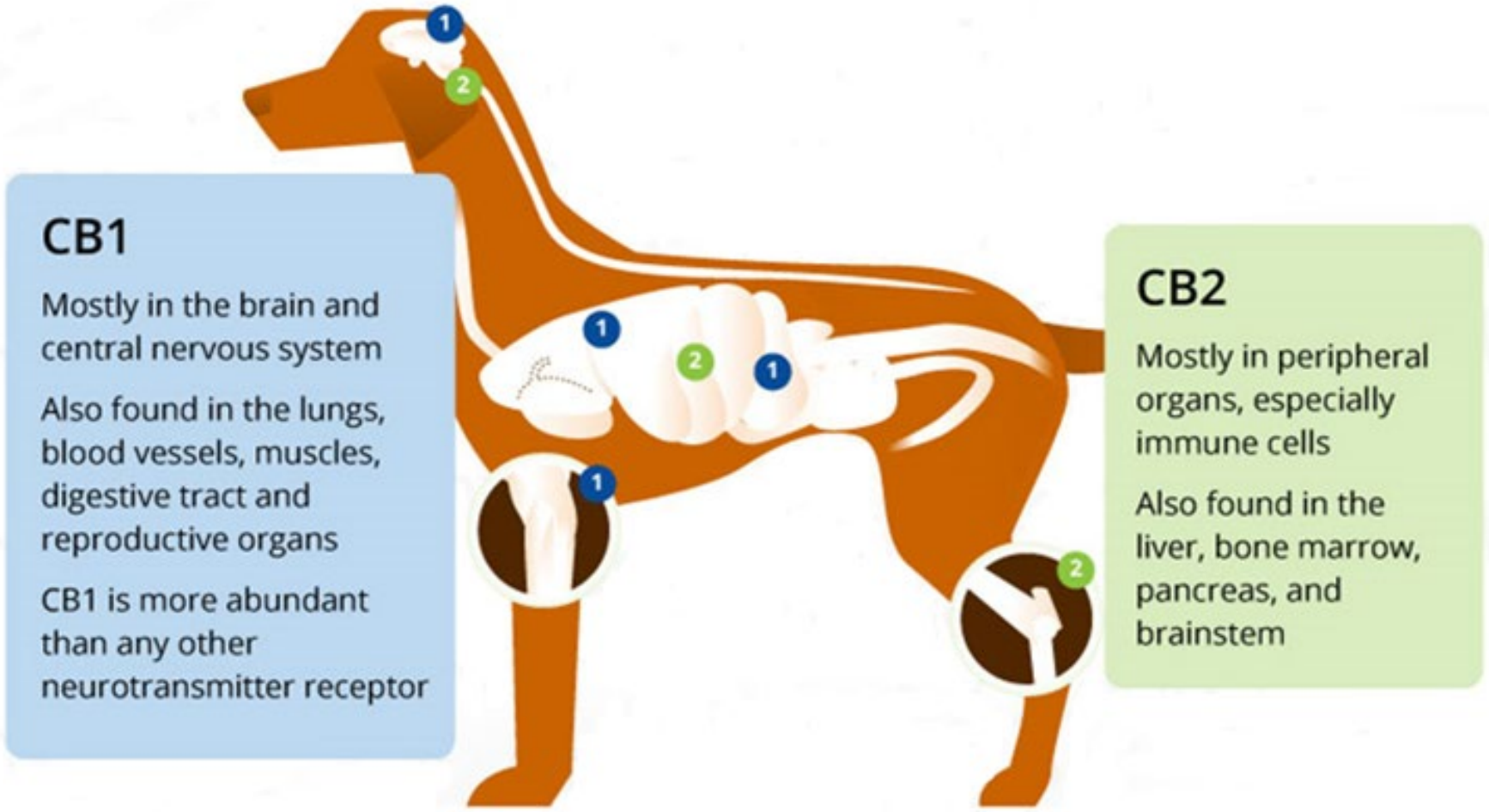
Endocannabinoids and CB Receptors





Maayah et al, BAA –molecular basis of dz, 2020

Endocannabinoid receptors



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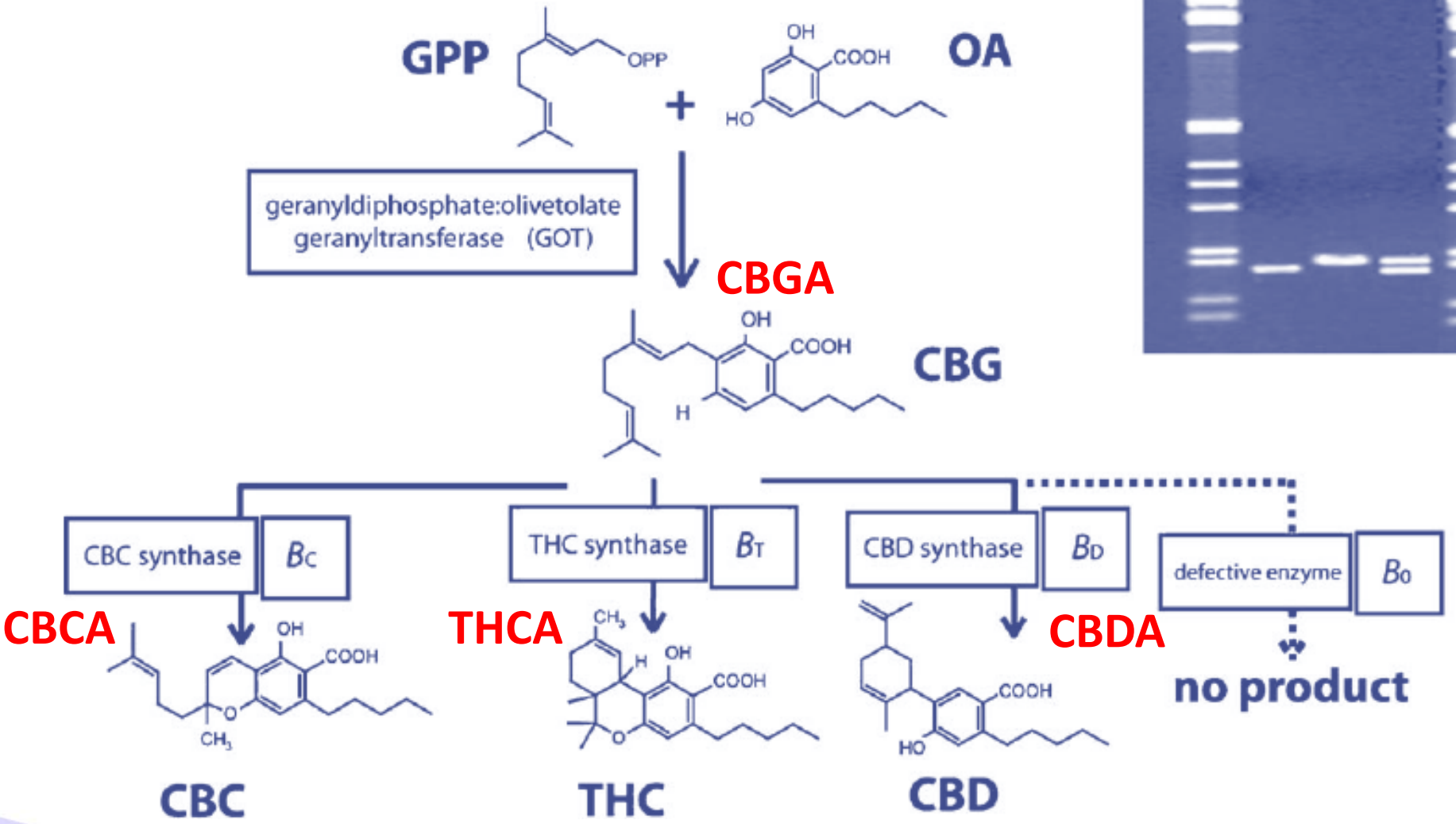
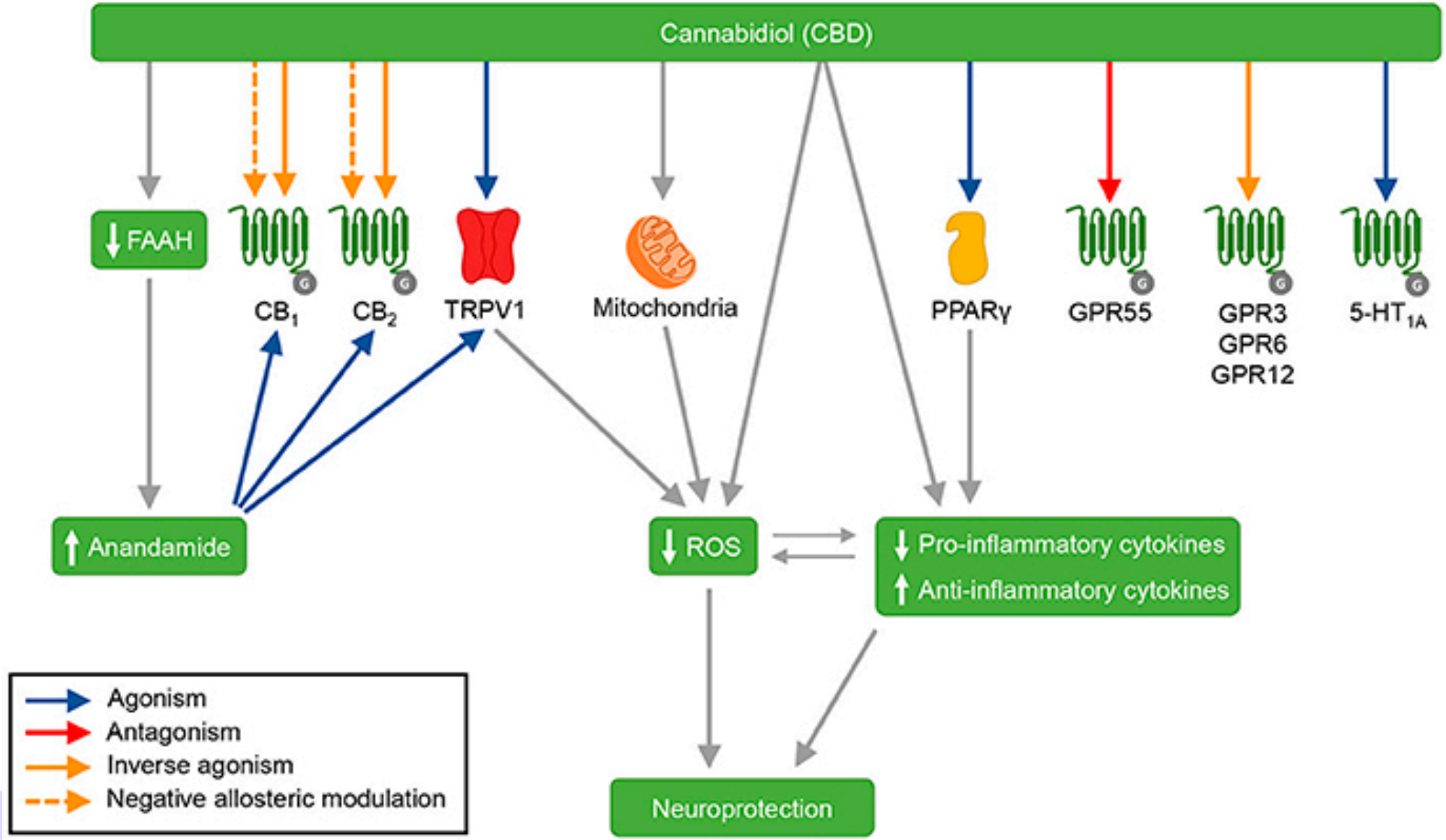
The biosynthetic pathways of hemp



The Endocannabinoidome



Peres, Front in Pharm, 2019

Cannabis vs Hemp vs Marijuana: What's the difference?

Cannabis/Hemp – Legal to distribute

- Cannabis
- Industrial hemp
- Grown for its tall, sturdy stalks
- Paper, textiles, biodegradable plastics, health food, fuel
- Low THC level < 0.3%

Marijuana/Cannabis

- Cannabis Sativa, Cannabis Indica
- Recreational and medical drug
- Restricted substance
- Leaves and flowering portions of the plants
- High THC level > 0.3%

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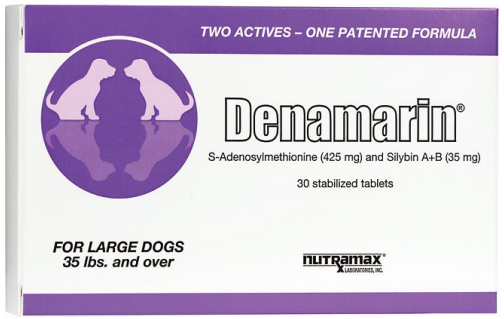
Allowed without FDA Approval



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Use of Hemp CBD Product in Veterinary Clinics

- Hemp CBD is not a controlled substance federally or in any state
- VMBs regulate veterinarians—not AVMA or other VMAs
- AAVSB recommends that veterinarians who use hemp CBD use products that:
  - Have a COA by an independent 3rd party lab
  - Tested for safety
  - Tested for accuracy of the label
  - Efficacy tested products preferred

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A Confusing Market

Penn Medicine News

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Home › News Releases › Penn Study Shows Nearly 70 Percent of Cannabidiol Extracts...

News Release

Penn Study Shows Nearly 70 Percent of Cannabidiol Extracts Sold Online Are Mislabeled

Mislabeling may lead to adverse effects for patients, including children with epilepsy

November 07, 2017

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Not all products are the same

Veterinary Medicine: Research and Reports

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Cannabinoid, Terpene, and Heavy Metal Analysis of 29 Over-the-Counter Commercial Veterinary Hemp Supplements

This article was published in the following Dove Press journal:
Veterinary Medicine: Research and Reports

Joseph J Wakshlag[1]
Stephen Cital[2]
Scott J Eaton[3]
Reece Prussin[2]
Christopher Hudalla[3]

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Purpose: The use of veterinary low tetrahydrocannabinol (THC) *Cannabis sativa* (ie, hemp) products has increased in popularity for a variety of pet ailments. Low-THC *Cannabis sativa* is federally legal for sale and distribution in the USA, and the rise in internet commerce has provided access to interested consumers, with minimal quality control.

Materials and Methods: We performed an internet word search of "hemp extract and dog" or "CBD product and dog" and analyzed 29 products that were using low-THC *Cannabis sativa* extracts in their production of supplements. All products were tested for major cannabinoids including cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC), cannabigerol (CBG), and other minor cannabinoids, as well as their carboxylic acid derivatives (CBDA, THCA, CBGA) using an ISO/IEC 17025 certified laboratory. Products were also tested for major terpenes and heavy metals to understand constituents in the hemp plants being extracted and distributed.

Results: All products were below the federal limit of 0.3% THC with variable amounts of CBD (0–88 mg/mL or g). Only two products did not supply a CBD or total cannabinoid concentration on their packaging or website, while 22/29 could supply a certificate of analysis (COA) from a third-party laboratory. Ten of the 27 products were within 10% of the total cannabinoid concentrations of their label claim with a median concentration of 93% of claims (0–154%). Heavy metal contamination was found in 4/29 products, with lead being the most prevalent contaminant (3/29).

Conclusion: The products analyzed had highly variable concentrations of CBD or total cannabinoids with only 18 of 29 being appropriately labeled according to current FDA non-medication, non-dietary supplement or non-food guidelines. Owners and veterinarians wanting to utilize CBD-rich *Cannabis sativa* products should be aware of low-concentration products and should obtain a COA enabling them to fully discuss the implications of use and calculated dosing before administering to pets.

Keywords: cannabinoid, hemp, supplement, cannabidiol, pet, terpene, oral

Introduction

The recent federal legalization and deregulation of low-THC *Cannabis sativa*, otherwise known as hemp, as a commercial crop in the USA has created a new supplement market for humans and pets alike that is largely unregulated.[1] The de-scheduling of low-THC *Cannabis sativa* derived extracts forced any oversight of products containing hemp derived CBD, and other cannabinoids, to the Food and Drug Administration (FDA).[2] The lack of clear FDA regulations and inconsistent state regulations being

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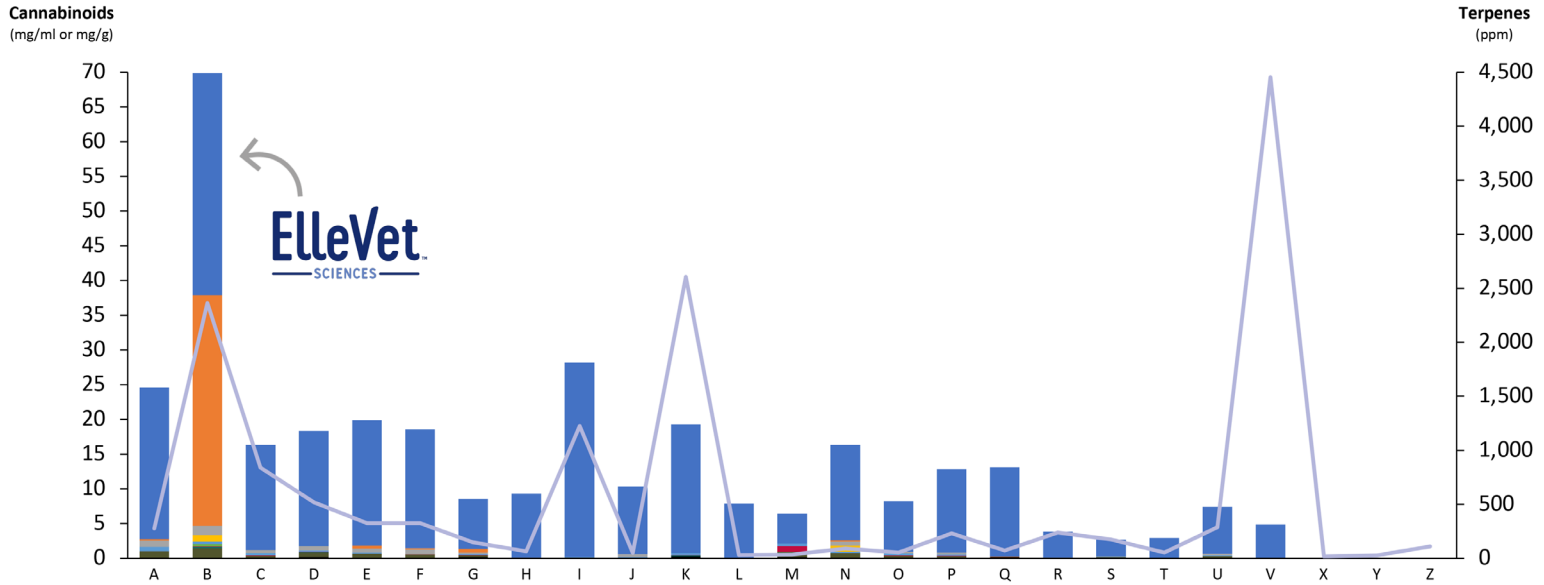

Lowest product cost — *Highest product cost*

Price per milligram	$0.05	$0.05	$0.08	$0.10	$0.11	$0.12	$0.12	$0.12	$0.14	$0.15	$0.16	$0.17	$0.18	$0.19	$0.21	$0.22	$0.34	$0.35	$0.37	$0.39	$0.40	$0.58	-	-	-
Price per day 0.75mg/kg dose BID for a 70lb dog (maintenance dose for joint discomfort)	$2.55	$2.56	$3.86	$4.73	$5.18	$5.61	$5.77	$5.89	$6.43	$6.89	$7.39	$8.05	$8.62	$9.25	$9.97	$10.65	$15.92	$16.55	$17.60	$18.37	$19.18	$27.34	-	-	-

Terpene · CBD · CBDA · THC · THCA · CBG · CBGA · CBN · THCV · CBC · CBDV

Based on a double blind third-party analysis

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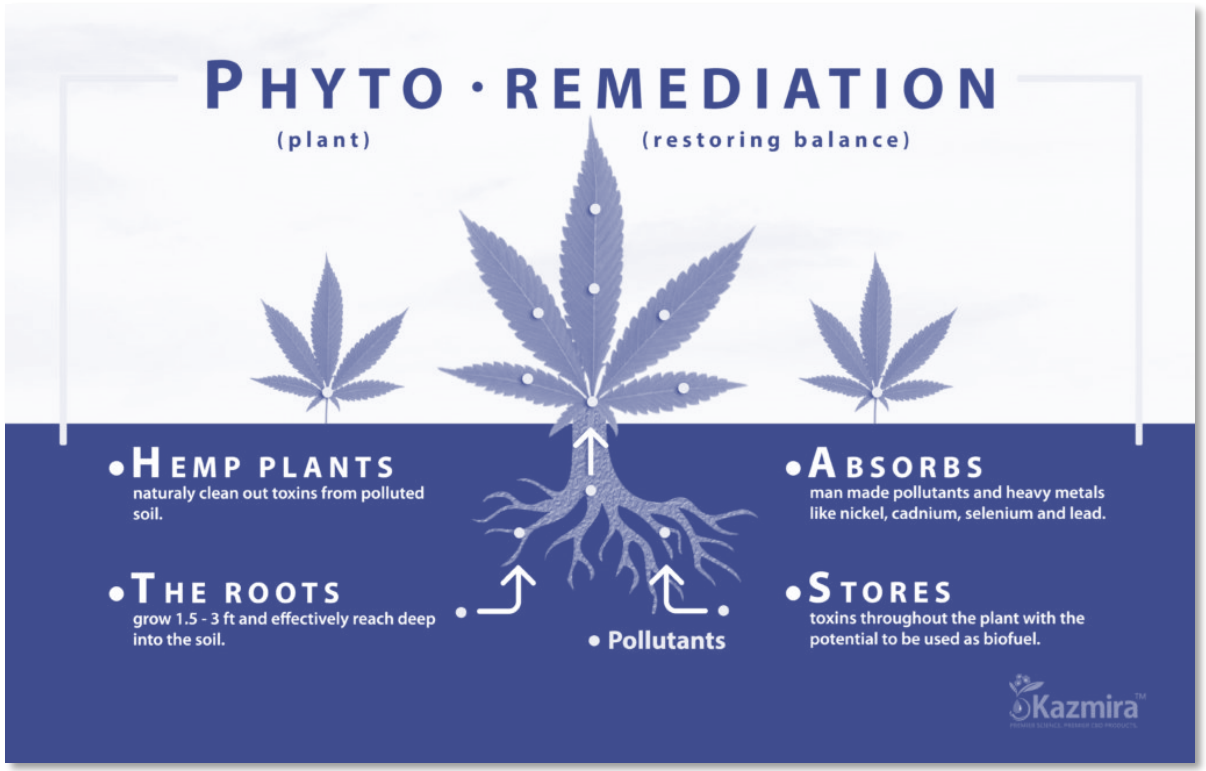
Heavy Metal Contamination

- 4 of 29 products were contaminated
- Hemp is often used for bioremediation of soil
- Increased uptake of mineral from soil
- Must ask for COA on final product
- Oils and other ingredients can be contaminated



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COA – from a certified 17025 laboratory

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EMAIL: INNOVATION@NOVA-ANALYTICLABS.COM
ME LICENSE #: TF284

CERTIFICATE OF ANALYSIS

** FOR QUALITY ASSURANCE PURPOSES. NOT A MAINE COMPLIANCE CERTIFICATE.*

VET STRENGTH CHEWS (EDIBLE SOLID) // THIS IS A REVISED COA ISSUED NOV 11, 2022

CLIENT: ELLEVET SCIENCES // BATCH: PASSED

BATCH NO.: 686007
MATRIX: EDIBLE SOLID
SAMPLE ID: NAL-221026-001
COLLECTED ON: OCT 26, 2022
RECEIVED ON: OCT 26, 2022
SAMPLE SIZE: 10 UNITS
SAMPLED BY: DANIEL HUGHES
RECEIVED BY: ZACHARY SMITH
SERVING SIZE: 6 G

CANNABINOID OVERVIEW

CBDA:	8.94 mg/srv
CBD:	8.64 mg/srv
TOTAL CANNABINOIDS:	19.4 mg/srv

MANUFACTURER INFO

MANUFACTURER
ELLEVET SCIENCES
200 JOHN ROBERTS RD, SUITE 4
SOUTH PORTLAND, MAINE 04106

LICENSE
200JRRS4
INDUSTRIAL HEMP

BATCH RESULT: PASSED

POTENCY	PASS
METALS	TESTED
MICROBIAL	TESTED
MYCOTOXINS	TESTED
PESTICIDES	TESTED
SOLVENTS	TESTED

CAN.1: POTENCY & CANNABINOID PROFILE BY HPLC-UV
PREPARATION: NOV 08, 2022 // ANALYSIS: NOV 08, 2022

ANALYTE	LIMIT	AMT	AMT	LOD/LOQ (%)	PASS/FAIL	ANALYTE	LIMIT	AMT	AMT	LOD/LOQ (%)	PASS/FAIL
CBC		0.00668 %	0.0668 mg/g	0.00104/0.00518	N/A	Δ⁸-THC		0.00675 %	0.0675 mg/g	0.00104/0.00518	N/A
CBCA		0.00568 %	0.0568 mg/g	0.00104/0.00518	N/A	Δ¹⁰-THC		ND	ND	0.00104/0.00518	N/A
CBD		0.144 %	1.44 mg/g	0.00104/0.00518	N/A	EXO-THC		ND	ND	0.00104/0.00518	N/A
CBDA		0.149 %	1.49 mg/g	0.00104/0.00518	N/A	THCA		< LOQ	< LOQ	0.00104/0.00518	N/A
CBDV		ND	ND	0.00104/0.00518	N/A	THCV		0.00600 %	0.0600 mg/g	0.00104/0.00518	N/A
CBDVA		< LOQ	< LOQ	0.00104/0.00518	N/A	TOTAL CBD**		ND	ND	0.00104/0.00518	N/A
CBG		ND	ND	0.00104/0.00518	N/A	TOTAL THC**		0.00675 %	0.0675 mg/g		N/A
CBGA		0.00556 %	0.0556 mg/g	0.00104/0.00518	N/A	CBD/SRV		0.275 %	2.75 mg/g		N/A
CBL		ND	ND	0.00104/0.00518	N/A	Δ⁸-THC/SRV		8.64 mg			N/A
CBLA		ND	ND	0.00104/0.00518	N/A	TOTAL THC/SRV**		0.410 mg			N/A
CBN		ND	ND	0.00104/0.00518	N/A	TOTAL CBD/SRV**		16.5 mg			N/A
CBNA		ND	ND	0.00104/0.00518	N/A						
Δ⁹-THC		ND	ND	0.00104/0.00518	N/A						

** TOTAL CBD = (CBDA X 0.877) + CBD
** TOTAL THC = (THCA X 0.877) + THC
Reported on an as received basis
1000 µg/g = 1 mg/g

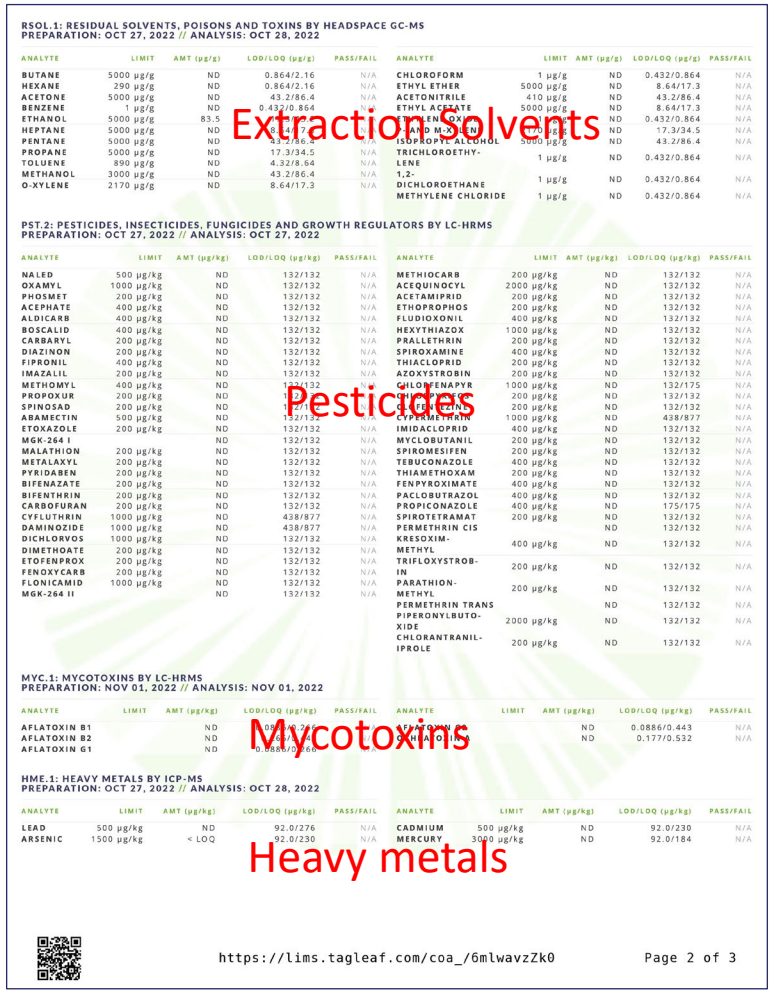
RESULTS CERTIFIED BY:
BARRY CHAFFIN
COO, NOVA ANALYTIC LABS
NOV 11, 2022

RESULTS CERTIFIED BY:
GREG NEWLAND
CSO, NOVA ANALYTIC LABS
NOV 11, 2022

RESULTS CERTIFIED BY:
CHRIS ALTOMARE
CEO, NOVA ANALYTIC LABS
NOV 11, 2022

https://lims.tagleaf.com/coa_/6mlwavzZk0

Cannabinoids



RSOL.1: RESIDUAL SOLVENTS, POISONS AND TOXINS BY HEADSPACE GC-MS
PREPARATION: OCT 27, 2022 // ANALYSIS: OCT 28, 2022

ANALYTE	LIMIT	AMT (µg/g)	LOD/LOQ (µg/g)	PASS/FAIL	ANALYTE	LIMIT	AMT (µg/g)	LOD/LOQ (µg/g)	PASS/FAIL
BUTANE	5000 µg/g	ND	0.864/2.16	N/A	CHLOROFORM	1 µg/g	ND	0.432/0.864	N/A
HEXANE	290 µg/g	ND	0.864/2.16	N/A	ETHYL ETHER	5000 µg/g	ND	8.64/17.3	N/A
ACETONE	5000 µg/g	ND	43.2/86.4	N/A	ACETONITRILE	410 µg/g	ND	43.2/86.4	N/A
BENZENE	1 µg/g	ND	0.432/0.864	N/A	ETHYL ACETATE	5000 µg/g	ND	8.64/17.3	N/A
ETHANOL	5000 µg/g	83.5	8.64/17.3	N/A	ETHYLENE OXIDE	1 µg/g	ND	0.432/0.864	N/A
HEPTANE	5000 µg/g	ND	8.64/17.3	N/A	M,P AND M-XYLENE	2170 µg/g	ND	17.3/34.5	N/A
PENTANE	5000 µg/g	ND	43.2/86.4	N/A	ISOPROPYL ALCOHOL	5000 µg/g	ND	43.2/86.4	N/A
PROPANE	5000 µg/g	ND	17.3/34.5	N/A	TRICHLOROETHYLENE	1 µg/g	ND	0.432/0.864	N/A
TOLUENE	890 µg/g	ND	4.32/8.64	N/A	1,2-DICHLOROETHANE	1 µg/g	ND	0.432/0.864	N/A
METHANOL	3000 µg/g	ND	43.2/86.4	N/A	METHYLENE CHLORIDE	1 µg/g	ND	0.432/0.864	N/A
O-XYLENE	2170 µg/g	ND	8.64/17.3	N/A					

Extraction Solvents

PST.2: PESTICIDES, INSECTICIDES, FUNGICIDES AND GROWTH REGULATORS BY LC-HRMS
PREPARATION: OCT 27, 2022 // ANALYSIS: OCT 27, 2022

ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL	ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL
NALED	500 µg/kg	ND	132/132	N/A	METHIOCARB	200 µg/kg	ND	132/132	N/A
OXAMYL	1000 µg/kg	ND	132/132	N/A	ACEQUINOCYL	2000 µg/kg	ND	132/132	N/A
PHOSMET	200 µg/kg	ND	132/132	N/A	ACETAMIPRID	200 µg/kg	ND	132/132	N/A
ACEPHATE	400 µg/kg	ND	132/132	N/A	ETHOPROPHOS	200 µg/kg	ND	132/132	N/A
ALDICARB	400 µg/kg	ND	132/132	N/A	FLUDIOXONIL	400 µg/kg	ND	132/132	N/A
BOSCALID	400 µg/kg	ND	132/132	N/A	HEXYTHIAZOX	1000 µg/kg	ND	132/132	N/A
CARBARYL	200 µg/kg	ND	132/132	N/A	PRALLETHRIN	200 µg/kg	ND	132/132	N/A
DIAZINON	200 µg/kg	ND	132/132	N/A	SPIROXAMINE	400 µg/kg	ND	132/132	N/A
FIPRONIL	400 µg/kg	ND	132/132	N/A	THIACLOPRID	200 µg/kg	ND	132/132	N/A
IMAZALIL	200 µg/kg	ND	132/132	N/A	AZOXYSTROBIN	200 µg/kg	ND	132/132	N/A
METHOMYL	400 µg/kg	ND	132/132	N/A	CHLORFENAPYR	1000 µg/kg	ND	132/175	N/A
PROPOXUR	200 µg/kg	ND	132/132	N/A	[illegible]	200 µg/kg	ND	132/132	N/A
SPINOSAD	200 µg/kg	ND	132/132	N/A	CLOFENTEZINE	200 µg/kg	ND	132/132	N/A
ABAMECTIN	500 µg/kg	ND	132/132	N/A	CYPERMETHRIN	1000 µg/kg	ND	438/877	N/A
ETOXAZOLE	200 µg/kg	ND	132/132	N/A	IMIDACLOPRID	400 µg/kg	ND	132/132	N/A
MGK-264 I		ND	132/132	N/A	MYCLOBUTANIL	200 µg/kg	ND	132/132	N/A
MALATHION	200 µg/kg	ND	132/132	N/A	SPIROMESIFEN	200 µg/kg	ND	132/132	N/A
METALAXYL	200 µg/kg	ND	132/132	N/A	TEBUCONAZOLE	400 µg/kg	ND	132/132	N/A
PYRIDABEN	200 µg/kg	ND	132/132	N/A	THIAMETHOXAM	200 µg/kg	ND	132/132	N/A
BIFENAZATE	200 µg/kg	ND	132/132	N/A	FENPYROXIMATE	400 µg/kg	ND	132/132	N/A
BIFENTHRIN	200 µg/kg	ND	132/132	N/A	PACLOBUTRAZOL	400 µg/kg	ND	132/132	N/A
CARBOFURAN	200 µg/kg	ND	132/132	N/A	PROPICONAZOLE	400 µg/kg	ND	175/175	N/A
CYFLUTHRIN	1000 µg/kg	ND	438/877	N/A	SPIROTETRAMAT	200 µg/kg	ND	132/132	N/A
DAMINOZIDE	1000 µg/kg	ND	438/877	N/A	PERMETHRIN CIS		ND	132/132	N/A
DICHLORVOS	1000 µg/kg	ND	132/132	N/A	KRESOXIM-METHYL	400 µg/kg	ND	132/132	N/A
DIMETHOATE	200 µg/kg	ND	132/132	N/A	TRIFLOXYSTROBIN	200 µg/kg	ND	132/132	N/A
ETOFENPROX	200 µg/kg	ND	132/132	N/A	PARATHION-METHYL	200 µg/kg	ND	132/132	N/A
FENOXYCARB	200 µg/kg	ND	132/132	N/A	PERMETHRIN TRANS		ND	132/132	N/A
FLONICAMID	1000 µg/kg	ND	132/132	N/A	PIPERONYLBUTOXIDE	2000 µg/kg	ND	132/132	N/A
MGK-264 II		ND	132/132	N/A	CHLORANTRANILIPROLE	200 µg/kg	ND	132/132	N/A

Pesticides

MYC.1: MYCOTOXINS BY LC-HRMS
PREPARATION: NOV 01, 2022 // ANALYSIS: NOV 01, 2022

ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL	ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL
AFLATOXIN B1		ND	0.0886/0.443	N/A	OCHRATOXIN A		ND	0.0886/0.443	N/A
AFLATOXIN B2		ND	0.0886/0.443	N/A	AFLATOXIN G2		ND	0.177/0.532	N/A
AFLATOXIN G1		ND	0.0886/0.443	N/A					

Mycotoxins

HME.1: HEAVY METALS BY ICP-MS
PREPARATION: OCT 27, 2022 // ANALYSIS: OCT 28, 2022

ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL	ANALYTE	LIMIT	AMT (µg/kg)	LOD/LOQ (µg/kg)	PASS/FAIL
LEAD	500 µg/kg	ND	92.0/276	N/A	CADMIUM	500 µg/kg	ND	92.0/230	N/A
ARSENIC	1500 µg/kg	< LOQ	92.0/230	N/A	MERCURY	3000 µg/kg	ND	92.0/184	N/A

Heavy metals

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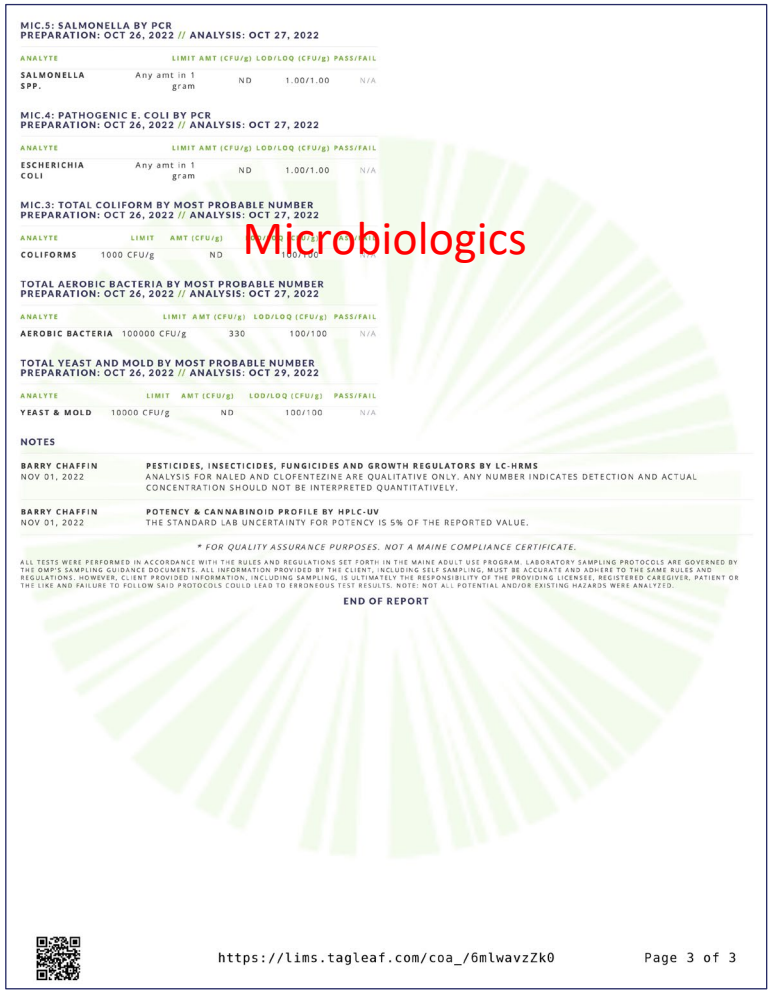


MIC.5: SALMONELLA BY PCR
PREPARATION: OCT 26, 2022 // ANALYSIS: OCT 27, 2022

ANALYTE	LIMIT	AMT (CFU/g)	LOD/LOQ (CFU/g)	PASS/FAIL
SALMONELLA SPP.	Any amt in 1 gram	ND	1.00/1.00	N/A

MIC.4: PATHOGENIC E. COLI BY PCR
PREPARATION: OCT 26, 2022 // ANALYSIS: OCT 27, 2022

ANALYTE	LIMIT	AMT (CFU/g)	LOD/LOQ (CFU/g)	PASS/FAIL
ESCHERICHIA COLI	Any amt in 1 gram	ND	1.00/1.00	N/A

MIC.3: TOTAL COLIFORM BY MOST PROBABLE NUMBER
PREPARATION: OCT 26, 2022 // ANALYSIS: OCT 27, 2022

ANALYTE	LIMIT	AMT (CFU/g)	LOD/LOQ (CFU/g)	PASS/FAIL
COLIFORMS	1000 CFU/g	ND	100/100	N/A

TOTAL AEROBIC BACTERIA BY MOST PROBABLE NUMBER
PREPARATION: OCT 26, 2022 // ANALYSIS: OCT 27, 2022

ANALYTE	LIMIT	AMT (CFU/g)	LOD/LOQ (CFU/g)	PASS/FAIL
AEROBIC BACTERIA	100000 CFU/g	330	100/100	N/A

TOTAL YEAST AND MOLD BY MOST PROBABLE NUMBER
PREPARATION: OCT 26, 2022 // ANALYSIS: OCT 29, 2022

ANALYTE	LIMIT	AMT (CFU/g)	LOD/LOQ (CFU/g)	PASS/FAIL
YEAST & MOLD	10000 CFU/g	ND	100/100	N/A

Microbiologics

NOTES

BARRY CHAFFIN
NOV 01, 2022
PESTICIDES, INSECTICIDES, FUNGICIDES AND GROWTH REGULATORS BY LC-HRMS
ANALYSIS FOR NALED AND CLOFENTEZINE ARE QUALITATIVE ONLY. ANY NUMBER INDICATES DETECTION AND ACTUAL CONCENTRATION SHOULD NOT BE INTERPRETED QUANTITATIVELY.

BARRY CHAFFIN
NOV 01, 2022
POTENCY & CANNABINOID PROFILE BY HPLC-UV
THE STANDARD LAB UNCERTAINTY FOR POTENCY IS 5% OF THE REPORTED VALUE.

** FOR QUALITY ASSURANCE PURPOSES. NOT A MAINE COMPLIANCE CERTIFICATE.*

ALL TESTS WERE PERFORMED IN ACCORDANCE WITH THE RULES AND REGULATIONS SET FORTH IN THE MAINE ADULT USE PROGRAM. LABORATORY SAMPLING PROTOCOLS ARE GOVERNED BY THE OMP'S SAMPLING GUIDANCE DOCUMENTS. ALL INFORMATION PROVIDED BY THE CLIENT, INCLUDING SELF-SAMPLING, MUST BE ACCURATE AND ADHERE TO THE SAME RULES AND REGULATIONS. HOWEVER, CLIENT PROVIDED INFORMATION, INCLUDING SAMPLING, IS ULTIMATELY THE RESPONSIBILITY OF THE PROVIDING LICENSEE, REGISTERED CAREGIVER, PATIENT OR THE LIKE AND FAILURE TO FOLLOW SAID PROTOCOLS COULD LEAD TO ERRONEOUS TEST RESULTS. NOTE: NOT ALL POTENTIAL AND/OR EXISTING HAZARDS WERE ANALYZED.

END OF REPORT

https://lims.tagleaf.com/coa_/6mlwavzZk0 Page 3 of 3

ElleVet SCIENCES

ElleVet – from Farm to Customer

Manufacturing

The ElleVet extract is further purified to meet all GMP requirements

Research

Products are supported by an expanding set of PK, safety and efficacy studies in different spp

Growing

The Unique Hemp CBD + CBDA extract used by ElleVet is grown and produced from a single proprietary hemp cultivar on our licensed farm in Colorado, USA

Testing

Products undergo comprehensive testing in-house and at 3rd party laboratories

ElleVet SCIENCES

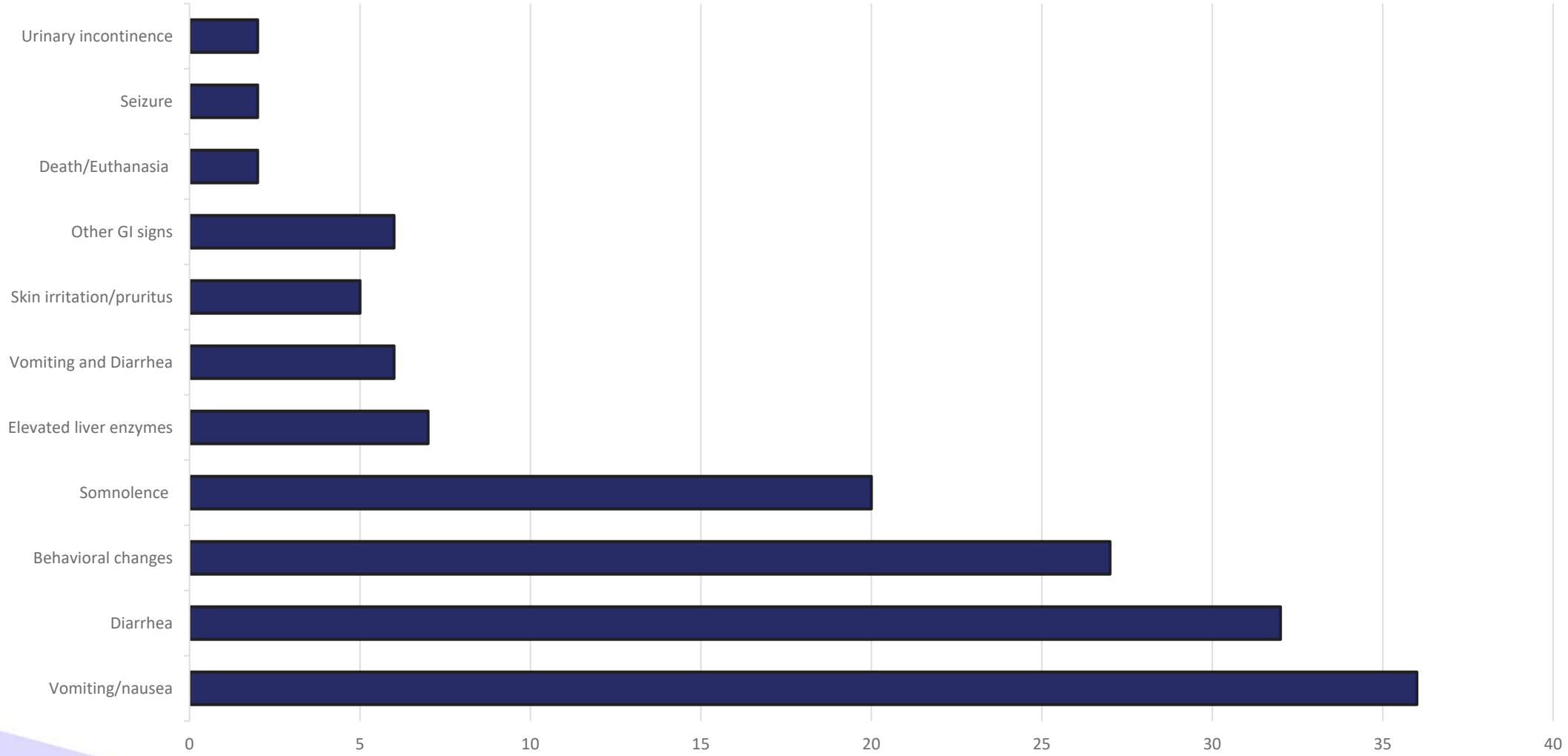
Pharmacovigilance beyond QC, literature monitoring/production…

Adverse event and product complaint management

- Safety data collection and coding
- Case management
- Monitoring
- Reporting
- Product recovery and analysis
- Communication

ElleVet SCIENCES

Classification of reported events per 10,000 unit sold



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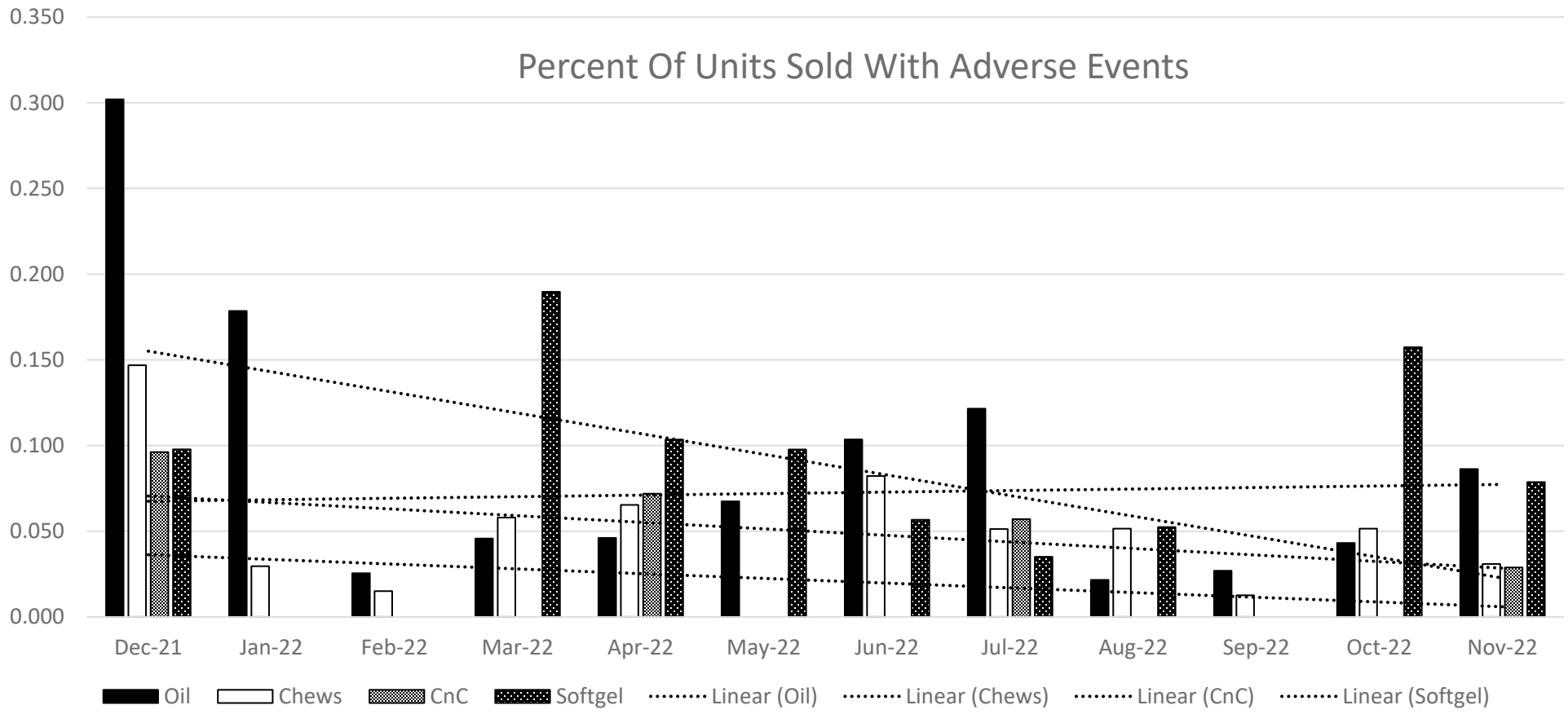
Adverse Reporting Ellevet



Reported Adverse Events

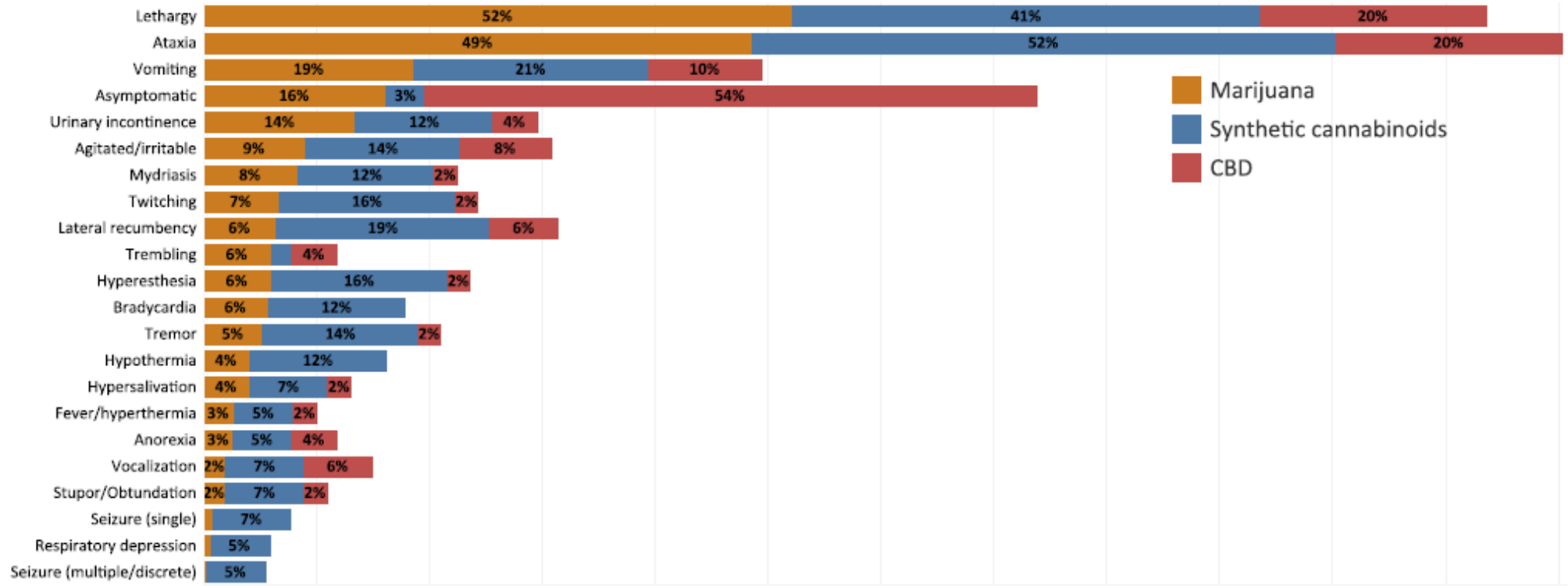


Fig. 1. Clinical signs associated with exposure to marijuana (ie, THC containing products, ~2200 cases), synthetic cannabinoids (~60 cases), and CBD (~50 cases) as reported to Pet Poison Helpline. Canines represent ~96% of the displayed data. Confirmation of exposure was not obtained in all cases, nor could co-ingestants such as chocolate or other toxicants be ruled out. Therefore, these data are meant to portray general trends only. Clinical signs reported in less than 5% of cases were excluded from this graphic.

ElleVet SCIENCES

NASC Reports per Administrations sold – 13 years

Year	Adverse events (report rate/million administrations sold)	Serious adverse events (report rate/million administrations sold)	Administrations sold[a]
2010	0.00	0.00	25,016
2011	0.00	0.00	29,098
2012	0.00	0.00	104,421
2013	7.82	0.00	255,642
2014	0.00	0.00	543,023
2015	0.00	0.00	894,762
2016	0.00	0.00	1,755,993
2017	0.13	0.00	7,938,081
2018	0.47	0.00	40,236,719
2019	0.87	0.00	115,449,344
2020	2.30	0.00	186,201,013
2021	2.15	0.02	286,466,260
2022	2.37	0.03	257,268,163
2023[b]	29.69	0.15	6,668,421
Grand Total	**2.19**	**0.01**	**903,835,956**

[a]Number of administrations sold was assumed to be a close approximation to administrations consumed.
[b]Usage data for 2023 is incomplete.

ElleVet SCIENCES

CBD long-term/dosing studies

British Journal of Pharmacology

British Journal of Pharmacology (2019) **176** 1506–1523

Themed Section: 8th European Workshop on Cannabinoid Research

RESEARCH PAPER

Species-specific susceptibility to cannabis-induced convulsions

Correspondence Gary J. Stephens, Hopkins Life Sciences Building, The University of Reading, Whiteknights, Reading, Berkshire R6AP, UK. E-mail: g.j.stephens@reading.ac.uk

Received 23 July 2017; **Revised** 24 January 2018; **Accepted** 5 February 2018

Benjamin J Whalley[1,4], Hong Lin[1], Lynne Bell[2], Thomas Hill[3], Amesha Patel[4], Roy A Gray[4], C Elizabeth Roberts[4], Orrin Devinsky[5], Michael Bazelot[4], Claire M Williams[2] and Gary J Stephens[1]

[1]Division of Pharmacology, School of Chemistry, Food and Nutritional Sciences, and Pharmacy, University of Reading, Reading, UK, [2]School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK, [3]Physiology & Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland, [4]GW Research Ltd, Salisbury, UK, and [5]Department of Neurology, Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, USA

BACKGROUND AND PURPOSE

Numerous claims are made for cannabis' therapeutic utility upon human seizures, but concerns persist about risks. A potent confounder is the presence of both Δ^9-tetrahydrocannabinol (THC), variously reported to be pro- and anticonvulsant, and cannabidiol (CBD), widely confirmed as anticonvulsant. Therefore, we investigated effects of prolonged exposure to differer THC/CBD cannabis extracts on seizure activity and associated measures of endocannabinoid (eCB) system signalling.

EXPERIMENTAL APPROACH

Cannabis extract effects on *in vivo* neurological and behavioural responses, and on bioanalyte levels, were measured in rats and d Extract effects on seizure activity were measured using electroencephalography telemetry in rats. eCB signalling was also investig using radioligand binding in cannabis extract-treated rats and treatment-naïve rat, mouse, chicken, dog and human tissue.

KEY RESULTS

mg/kg QD; 15/sex/group + 10/sex/group for C and HD recovery), no dose-limiting toxicity was observed. The primary target organ was liver, with hepatocellular hypertrophy, accompanied by slight (1.2-1.4 fold) increases in ALT and ALP, observed at the MD and HD in males and females. No effects were observed on sperm parameters; interstitial cell hyperplasia in ovary was observed at the MD and HD. In the 39-week study (0, 10, 50, or 100 mg/kg QD; 4/sex/group + 2/sex for C and HD recovery), there were no deaths; the only clinical sign was soft/liquid/mucoid feces. Decreases in absolute body weight (compared to C) were observed at all doses in males (5, 15, and 12% at LD, MD, and HD, respectively) and females (22, 29, and 32% at LD, MD, and HD, respectively). As in rat, the primary target organ was liver, with hepatocellular hypertrophy detected at all doses (dose-related only in males), accompanied by increases in ALT (slight) and ALP (up to 8-fold).

The toxicokinetic (TK) data at the highest doses tested in rat and dog and at the maximum recommended dose in humans are summarized in the following table.

SPECIES	DOSE (mg/kg)	SEX	CBD		7-OH-CBD		7-COOH-CBD	
			C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng*hr/mL)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng*hr/mL)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng*hr/mL)
Rat	150	M	6160	60000	334	2560	4180	37100
		F	7530	67500	625	6730	2710	40500
Dog	100	M	2570	20500	134	1380	82.1	994
		F	2660	22400	117	1090	137	1560
Human*	10 BID	M/F	--	2790	--	1562	--	137886

*Data were extrapolated (by the sponsor) from data in humans at 750 mg BID, following the first daily dose (Study GWEP1544).

ElleVet SCIENCES

Pharmacokinetics & Safety in Dogs & Cats (Deabold, 2019)

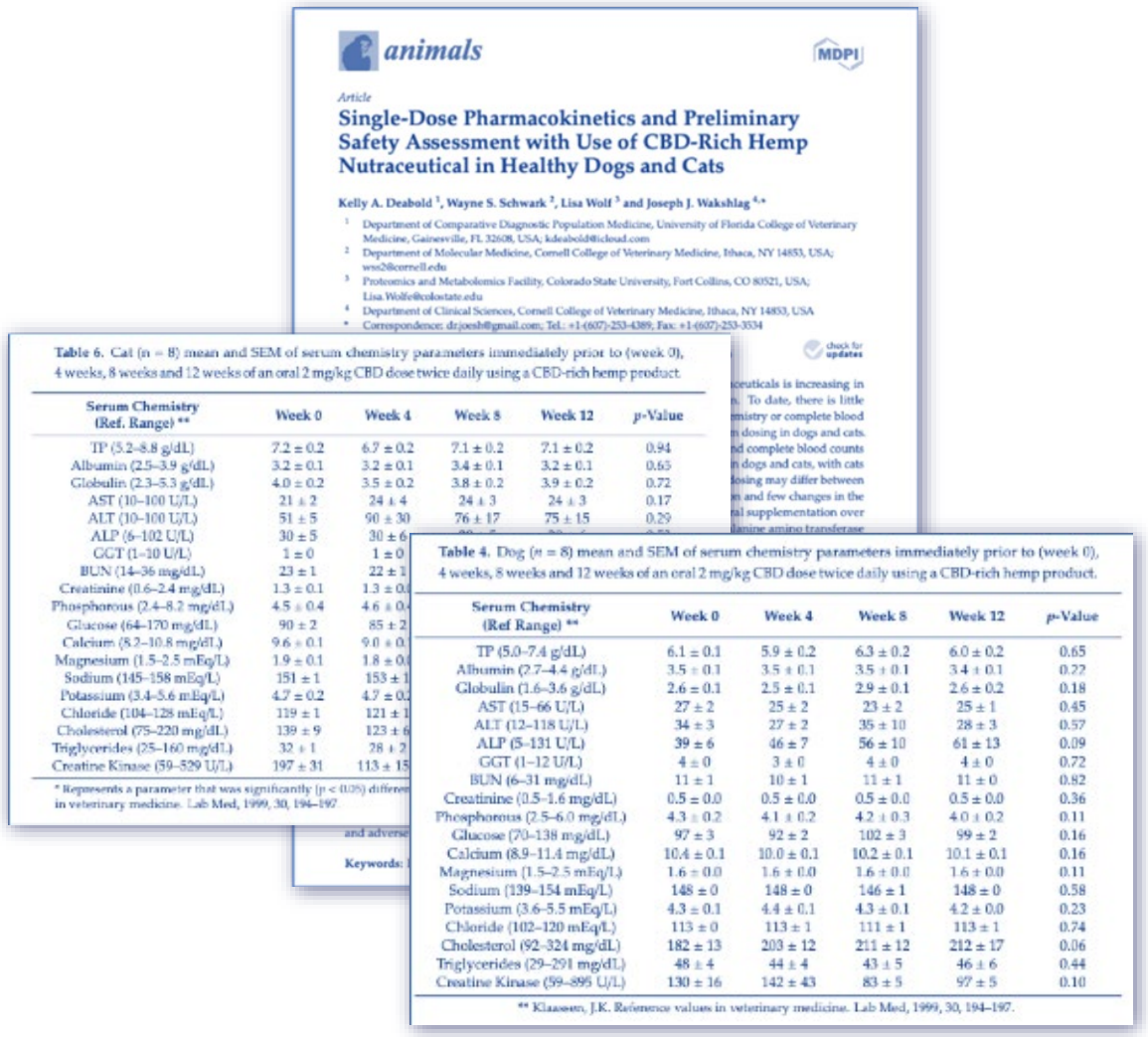
8 Dogs | 2mg/Kg Total cannabinoids | BID | 12wks

- ElleVet Mobility Chews
- mean maximum concentration (Cmax) of 301 ng/mL
- area under the curve (AUC) of 1297 ng-h/mL
- time to maximal concentration (Tmax) of 1.4 h

8 Cats | 2mg/Kg Total cannabinoids | BID | 12wks

- ElleVet blend-infused fish oil
- mean maximum concentration (Cmax) of 43 ng/mL
- area under the curve (AUC) of 164 ng-h/mL
- time to maximal concentration (Tmax) of 2h

UF UNIVERSITY of FLORIDA



animals — MDPI

Article

Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats

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[3] Proteomics and Metabolomics Facility, Colorado State University, Fort Collins, CO 80521, USA; Lisa.Wolfe@colostate.edu
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Table 6. Cat (n = 8) mean and SEM of serum chemistry parameters immediately prior to (week 0), 4 weeks, 8 weeks and 12 weeks of an oral 2 mg/kg CBD dose twice daily using a CBD-rich hemp product.

Serum Chemistry (Ref. Range) **	Week 0	Week 4	Week 8	Week 12	p-Value
TP (5.2–8.8 g/dL)	7.2 ± 0.2	6.7 ± 0.2	7.1 ± 0.2	7.1 ± 0.2	0.94
Albumin (2.5–3.9 g/dL)	3.2 ± 0.1	3.2 ± 0.1	3.4 ± 0.1	3.2 ± 0.1	0.65
Globulin (2.3–5.3 g/dL)	4.0 ± 0.2	3.5 ± 0.2	3.8 ± 0.2	3.9 ± 0.2	0.72
AST (10–100 U/L)	21 ± 2	24 ± 4	24 ± 3	24 ± 3	0.17
ALT (10–100 U/L)	51 ± 5	90 ± 30	76 ± 17	75 ± 15	0.29
ALP (6–102 U/L)	30 ± 5	30 ± 6			
GGT (1–10 U/L)	1 ± 0	1 ± 0			
BUN (14–36 mg/dL)	23 ± 1	22 ± 1			
Creatinine (0.6–2.4 mg/dL)	1.3 ± 0.1	1.3 ± 0.			
Phosphorous (2.4–8.2 mg/dL)	4.5 ± 0.4	4.6 ± 0.			
Glucose (64–170 mg/dL)	90 ± 2	85 ± 2			
Calcium (8.2–10.8 mg/dL)	9.6 ± 0.1	9.0 ± 0.			
Magnesium (1.5–2.5 mEq/L)	1.9 ± 0.1	1.8 ± 0.			
Sodium (145–158 mEq/L)	151 ± 1	153 ± 1			
Potassium (3.4–5.6 mEq/L)	4.7 ± 0.2	4.7 ± 0.			
Chloride (104–128 mEq/L)	119 ± 1	121 ± 1			
Cholesterol (75–220 mg/dL)	139 ± 9	123 ± 6			
Triglycerides (25–160 mg/dL)	32 ± 1	28 ± 2			
Creatine Kinase (59–529 U/L)	197 ± 31	113 ± 15			

* Represents a parameter that was significantly ($p < 0.05$) differen
in veterinary medicine. Lab Med, 1999, 30, 194–197.

Keywords:

Table 4. Dog (n = 8) mean and SEM of serum chemistry parameters immediately prior to (week 0), 4 weeks, 8 weeks and 12 weeks of an oral 2 mg/kg CBD dose twice daily using a CBD-rich hemp product.

Serum Chemistry (Ref Range) **	Week 0	Week 4	Week 8	Week 12	p-Value
TP (5.0–7.4 g/dL)	6.1 ± 0.1	5.9 ± 0.2	6.3 ± 0.2	6.0 ± 0.2	0.65
Albumin (2.7–4.4 g/dL)	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	3.4 ± 0.1	0.22
Globulin (1.6–3.6 g/dL)	2.6 ± 0.1	2.5 ± 0.1	2.9 ± 0.1	2.6 ± 0.2	0.18
AST (15–66 U/L)	27 ± 2	25 ± 2	23 ± 2	25 ± 1	0.45
ALT (12–118 U/L)	34 ± 3	27 ± 2	35 ± 10	28 ± 3	0.57
ALP (5–131 U/L)	39 ± 6	46 ± 7	56 ± 10	61 ± 13	0.09
GGT (1–12 U/L)	4 ± 0	3 ± 0	4 ± 0	4 ± 0	0.72
BUN (6–31 mg/dL)	11 ± 1	10 ± 1	11 ± 1	11 ± 0	0.82
Creatinine (0.5–1.6 mg/dL)	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.36
Phosphorous (2.5–6.0 mg/dL)	4.3 ± 0.2	4.1 ± 0.2	4.2 ± 0.3	4.0 ± 0.2	0.11
Glucose (70–138 mg/dL)	97 ± 3	92 ± 2	102 ± 3	99 ± 2	0.16
Calcium (8.9–11.4 mg/dL)	10.4 ± 0.1	10.0 ± 0.1	10.2 ± 0.1	10.1 ± 0.1	0.16
Magnesium (1.5–2.5 mEq/L)	1.6 ± 0.0	1.6 ± 0.0	1.6 ± 0.0	1.6 ± 0.0	0.11
Sodium (139–154 mEq/L)	148 ± 0	148 ± 0	146 ± 1	148 ± 0	0.58
Potassium (3.6–5.5 mEq/L)	4.3 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.2 ± 0.0	0.23
Chloride (102–120 mEq/L)	113 ± 0	113 ± 1	111 ± 1	113 ± 1	0.74
Cholesterol (92–324 mg/dL)	182 ± 13	203 ± 12	211 ± 12	212 ± 17	0.06
Triglycerides (29–291 mg/dL)	48 ± 4	44 ± 4	43 ± 5	46 ± 6	0.44
Creatine Kinase (59–895 U/L)	130 ± 16	142 ± 43	83 ± 5	97 ± 5	0.10

** Klaassen, J.K. Reference values in veterinary medicine. Lab Med, 1999, 30, 194–197.

ElleVet SCIENCES

Safety? 6 month Dogs – 4 mg/kg SID

Long-term daily feeding of cannabidiol is well-tolerated by healthy dogs

Sophie Bradley, Scott Young, Anne Marie Bakke, Lucy Holcombe, Daniel Waller, Alysia Hunt, Kathleen Pinfold, Phillip Watson and Darren W. Logan*

Waltham Petcare Science Institute, Waltham-on-the-Wolds, Melton Mowbray, United Kingdom

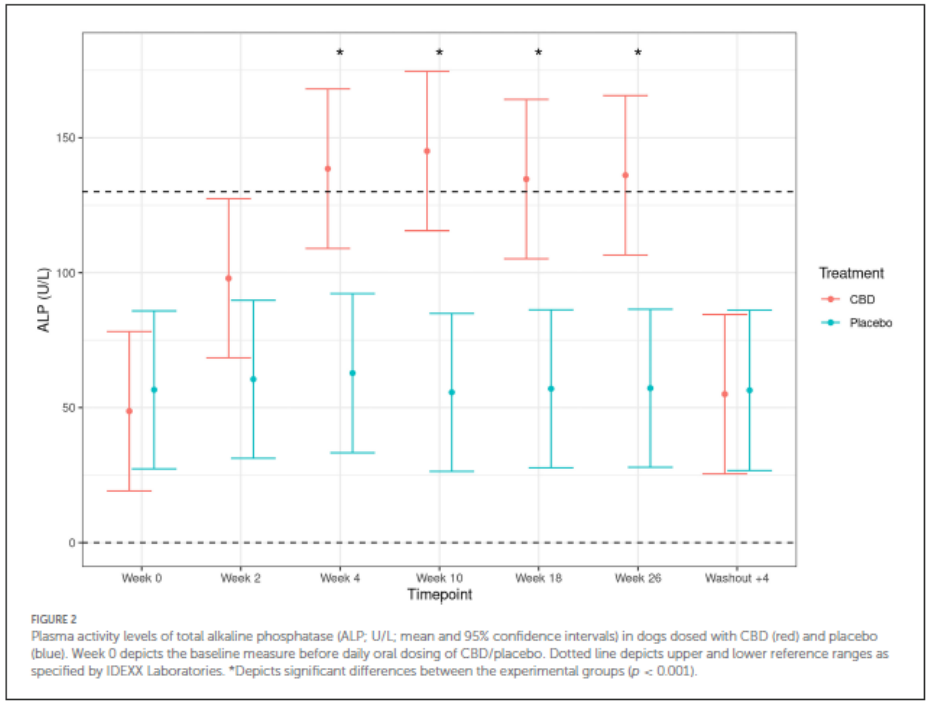

FIGURE 2
Plasma activity levels of total alkaline phosphatase (ALP; U/L; mean and 95% confidence intervals) in dogs dosed with CBD (red) and placebo (blue). Week 0 depicts the baseline measure before daily oral dosing of CBD/placebo. Dotted line depicts upper and lower reference ranges as specified by IDEXX Laboratories. *Depicts significant differences between the experimental groups ($p < 0.001$).

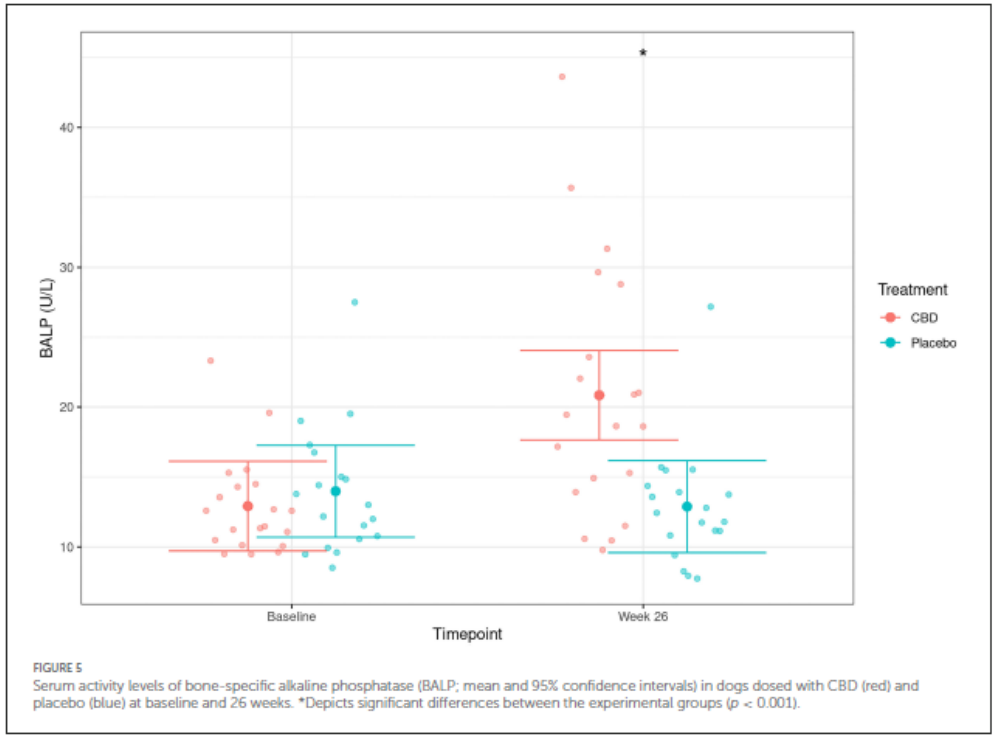

FIGURE 5
Serum activity levels of bone-specific alkaline phosphatase (BALP; mean and 95% confidence intervals) in dogs dosed with CBD (red) and placebo (blue) at baseline and 26 weeks. *Depicts significant differences between the experimental groups ($p < 0.001$).

ElleVet SCIENCES

Being Cost Conscious

	A	B	C	ElleVet	D	E
mg/mL	12.5	4	10.6	70	12.8	4.8
Days product lasts*	6	2	9.4	31.1	6	2.3
Price	$132	$39.95	$65.00	$129.99	$85.99	$84.08
$ per mg	$0.33	$0.34	$0.11	$0.06	$0.23	$0.56

*Days calculated using 1mg/kg for a 70lb dog

ElleVet SCIENCES

"Cannabis is a heterogenous botanical mixture and the results from one study cannot to be applied generally to other plants or products."

– Dr. Ethan Russo

ElleVet SCIENCES

The beginning of a Journey in Vet Med!

- Need to understand oral availability.
- Need to understand toxicity (covered last week).
- Need to understand Drug interactions.
- Need to understand the synergies with other meds.
- There is a lot to understand and we have many species!

ElleVet SCIENCES

Can Dogs Absorb CBD after oral consumption?

0090-9556/88/1603-0469$02.00/0
DRUG METABOLISM AND DISPOSITION
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PHARMACOKINETICS OF CANNABIDIOL IN DOGS

EMIL SAMARA, MEIR BIALER, AND RAPHAEL MECHOULAM

Department of Pharmacy (E.S., M.B.) and Department of Natural Products (E.S., R.M.), School of Pharmacy, Hebrew University

(Received August 10, 1987; accepted November 16, 1987)

ABSTRACT:

Cannabidiol (CBD) is one of the major nonpsychoactive cannabinoids produced by *Cannabis sativa L.* Recent studies have shown that CBD has a high protective index, comparable to that of phenobarbital and phenytoin. Because CBD has been reported to possess both anticonvulsant and antiepileptic activity, its pharmacokinetics were studied in dogs after the administration of two iv doses (45 and 90 mg) and one oral dose (180 mg) to dogs. After iv administration, CBD was rapidly distributed, followed by a prolonged elimination. It has a terminal half-life of 9 hr. CBD plasma levels declined in a triphasic fashion. The total body clearance of CBD was 17 liters/hr (after the 45-mg dose) and 16 liters/hr (after the 90-mg dose). This clearance value, after its normalization to blood clearance using mathematical equations, approaches the value of the hepatic blood flow; the extraction ratio in the liver is 0.74. CBD was observed to have a large volume of distribution, approximately 100 liters. In the dose range of 45 to 90 mg, the increase in the AUC was proportional to the dose, a fact that indicates that the pharmacokinetic profile of CBD in this dose range was not dose dependent. In three of the six dogs studied, CBD could not be detected in the plasma after oral administration. In the other three, the oral bioavailability ranged from 13 to 19%. The results of this study show that CBD is barely absorbed after oral administration to dogs. This low bioavailability may be due to a first pass effect.

DRUG METABOLISM & DISPOSITION

CBD[1] is one of the major cannabinoids produced by *Cannabis sativa L.* (1) and, although it was first isolated in 1940, its structure was elucidated only 23 years later (2). In contrast to the highly psychoactive major compound, THC, CBD has virtually no psychoactive propeties in humans (3–5). Nevertheless, CBD possesses anticonvulsant activity in both animals and man (6, 7). Recent studies have shown that CBD has a high protective index, comparable to that of phenobarbital and phenytoin (6–8). Despite the fact that CBD is one of the main constituents of cannabis and the recent surge of interest in its medical applications, few reports have been published on its pharmacokinetics (9, 10).

The present study was undertaken to investigate the pharmacokinetics of CBD in dogs after the administration of two iv doses (45 and 90 mg) and one oral dose (180 mg).

Materials and Methods

The experiments were conducted in six dogs (mongrels), three males and three females, all weighing between 16 and 24 kg. Each dog received, at separate times and in a crossover design, iv injections of CBD (45 or 90 mg in 1.5 ml of 70% alcohol) into the cephalic vein and an oral gelatin capsule containing 180 mg of CBD (in raw material form). Venous blood samples (8 ml) were collected via an indwelling catheter from the other cephalic vein at 0, 2, 5, 10, 15, 20, 30, 40, and 50 min and 1.0, 1.25, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hr after each of the two iv injections. After oral administration, the sampling times were the same except for the first hour, in which blood was first withdrawn only 30 min after drug administration. A washout period of 3 weeks was allowed between any two consecutive studies. Plasma was immediately separated by centrifugation at 7000 rpm for 15 min and stored at −20°C. Before assaying, the plasma was allowed to reach room temperature and the residual clot was removed. Plasma levels of CBD were assayed by an HPLC assay that we have already reported in detail (11).

The linear terminal slope of log C (CBD plasma concentration) *vs.* t (time) was calculated by the method of least squares. The terminal $t_{1/2}$ of CBD was calculated from the quotient: (0.69)/(terminal slope). The AUC (area under the C *vs.* t curve) was calculated by using the trapezoidal rule with extrapolation to infinity, by dividing the last experimental plasma concentration by the terminal slope (12).

The total body clearance of CBD (CL) was calculated from the dose-quotient and the AUC. The volume of distribution (V) was calculated from the ratio of the clearance and the linear terminal slope. The volume of distribution at steady state (V_{ss}) and the mean residence time (MRT) were calculated by using equations 1 and 2 (13–15).

$$V_{ss} = \frac{D \cdot \text{AUMC}}{(\text{AUC})^2} \quad (1)$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \quad (2)$$

AUMC is the area under the curve of the product of t (time) and C (plasma drug concentration) *vs.* (t), from time zero to infinity. AUMC was calculated by the trapezoidal rule with extrapolation to infinity. All pharmacokinetic parameters were calculated in a noncompartmental manner, based on the statistical moment theory (15, 16).

The blood-plasma concentration ratio (17) of CBD (partition study) was determined at room temperature by spiking known various amounts of CBD in seven samples of fresh blood taken from a dog before drug administration. CBD concentration ranged from 50 to 1000 ng/ml. Each blood sample was centrifuged immediately after spiking and the plasma was separated according to the procedure mentioned above. Plasma levels of CBD were determined by HPLC assay (11). The mean blood cell plasma concentration ratio was calculated by means of the following formula:

$$\frac{C_b}{C_p} = \frac{C_w}{C_p} \times \text{HCT} + (1 - \text{HCT}) \quad (3)$$

where C_b/C_p is the blood-plasma concentration ratio, C_w/C_p is the blood cell-plasma concentration ratio, and HCT is the hematocrit.

This paper is taken from the doctoral dissertation of Mr. Emil Samara, submitted in partial fulfillment of the Ph.D. requirements of the Hebrew University of Jerusalem.

[1] Abbreviations used are CBD, cannabidiol; THC, Δ¹-tetrahydrocannabinol; MFO, mixed function oxidases.

Send reprint requests to: Meir Bialer, Department of Pharmacy, School of Pharmacy, Hebrew University, POB 12065, Jerusalem 91120, Israel.

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Downloaded from dmd.aspetjournals.org at ASPET Journals on May 4, 2020

- Major reason hemp was not well studied was 1980's study suggesting absorption was not all that good
- Suggested that a powder in a capsule showed approximately 0-13% absorption
- Was provided in a capsule form from Raw Material – unsure if pure
- Interestingly participated in a study and found dogs passing capsules in stool

ElleVet SCIENCES

Dog PK work!

Article

Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs

Lisa R. Bartner, Stephanie McGrath, Sangeeta Rao, Linda K. Hyatt, Luke A. Wittenburg

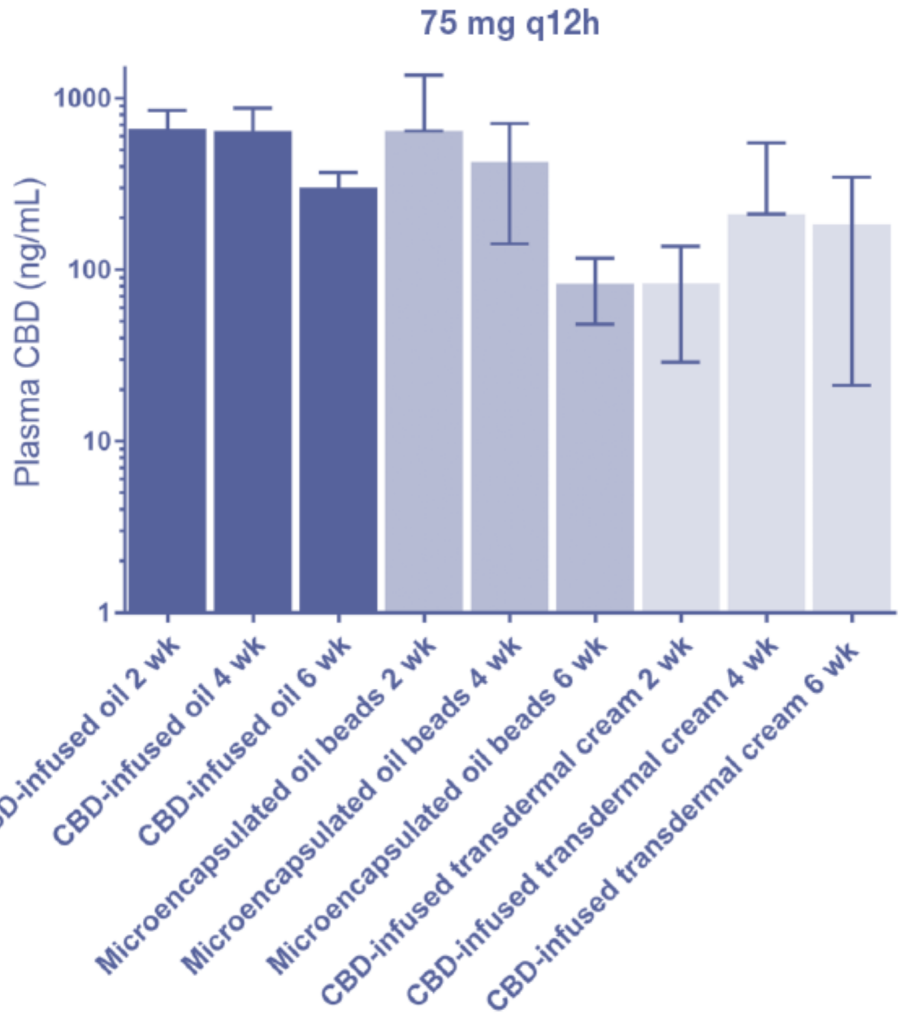
Table I. Dosing regimen for CBD administered to healthy beagle dogs.

Group (5 dogs/group)	Delivery method	Approximate dose (mg/kg body weight per day)	Dose (mg q12h)
1a	CBD-infused transdermal cream	10	75
1b	CBD-infused transdermal cream	20	150
2a	Microencapsulated oil beads	10	75
2b	Microencapsulated oil beads	20	150
3a	CBD-infused oil	10	75
3b	CBD-infused oil	20	150

ElleVet SCIENCES

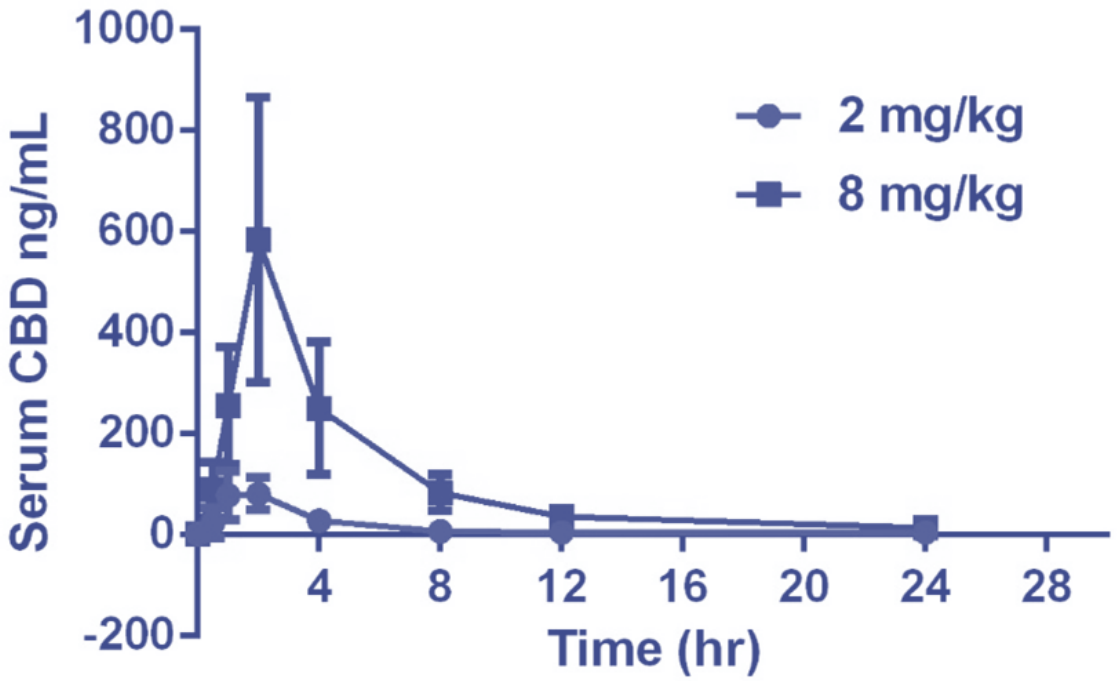
2,4, and 6 weeks of dosing!

- Steady State pharmacokinetics at 10 mg/kg every 12 hrs
- Oil appears to reveal ave. 500 ng/ml
- 500 ng/mL = 1.4 uM
- Important since presumed receptors iterations are between 0.1-1 uM
  - So presumed above 50 ng/mL in blood should be enough for receptor interactions.
- Consequences of oral dosing for 6 weeks – elevations in ALP and some ALT

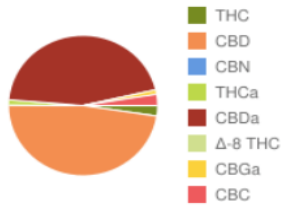


ElleVet SCIENCES

Serum concentration (ng/ml) of 2mg/kg and 8mg/kg oral dose CBD-CBDA (50:50 mix) oil over time!



Cannabinoid	mg per serving
THC	1.53mg
CBD	30.44mg
CBN	<0.1mg
THCa	0.76mg
CBDa	28.73mg
Δ-8 THC	<0.1mg
CBGa	0.66mg
THCv	<0.1mg
CBDv	<0.1mg
CBC	1.65mg
Total	**63.77mg**



	2 mg/kg oral	8 mg/kg oral
Cmax (ng/mL)	102	591
AUC (ng-h/mL)	367	2658
T ½ elim	4.2	4.2

ElleVet SCIENCES

Cannabinoids and Potential Therapeutically?

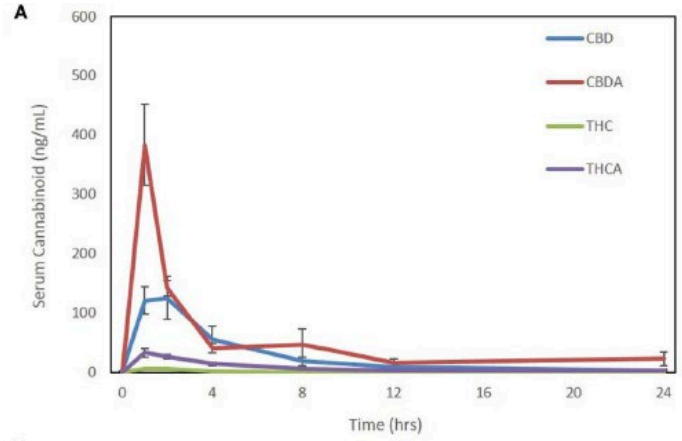
- Cannabidiol (CBD) – potential therapeutic (inflammation, neuroprotection, neuropathic pain)
- Cannabidiolic Acid (CBDA) – potential therapeutic (inflammation, neuroprotection, neuropathic pain)
- D9 tetrahydrocannabinol (THC) – potential psychotropic actions after metabolism.
- 11OH-Tetrahydrocannabinol (11OH-THC) – psychotropic active metabolite
- Tetrahydrocannabinolic acid (THCA) – potential therapeutic (neuroprotective)
- 7OH and 7COOH-cannabidiol (typical metabolites in humans)

ElleVet SCIENCES

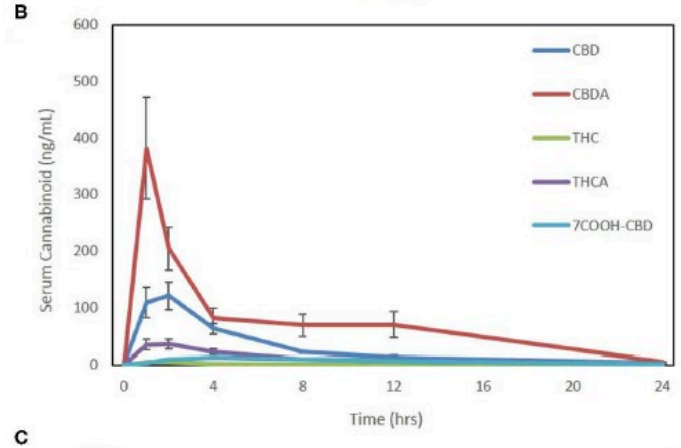
24 Hour Pharmacokinetics

- Metabolites of THC, 11-OH-THC, 7-OH-CBD, and COOH-THC-Glu all below the lower limit of quantitation
- Oil B with lecithin provides a larger AUC due to a lower level of absorption or less elimination from 4-24 hrs

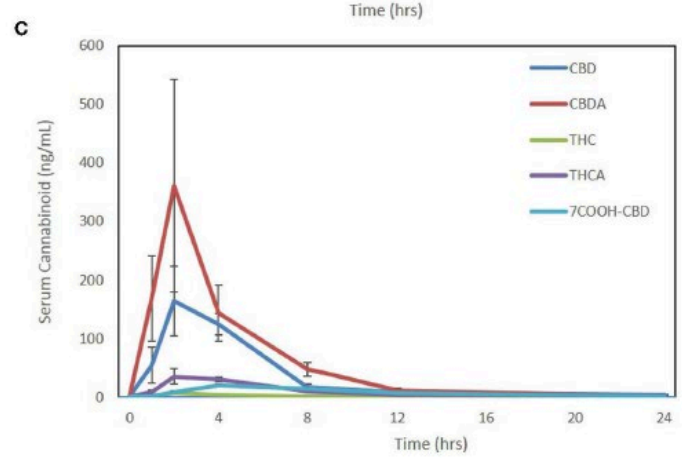
25% MCT Oil



25% Lecithin



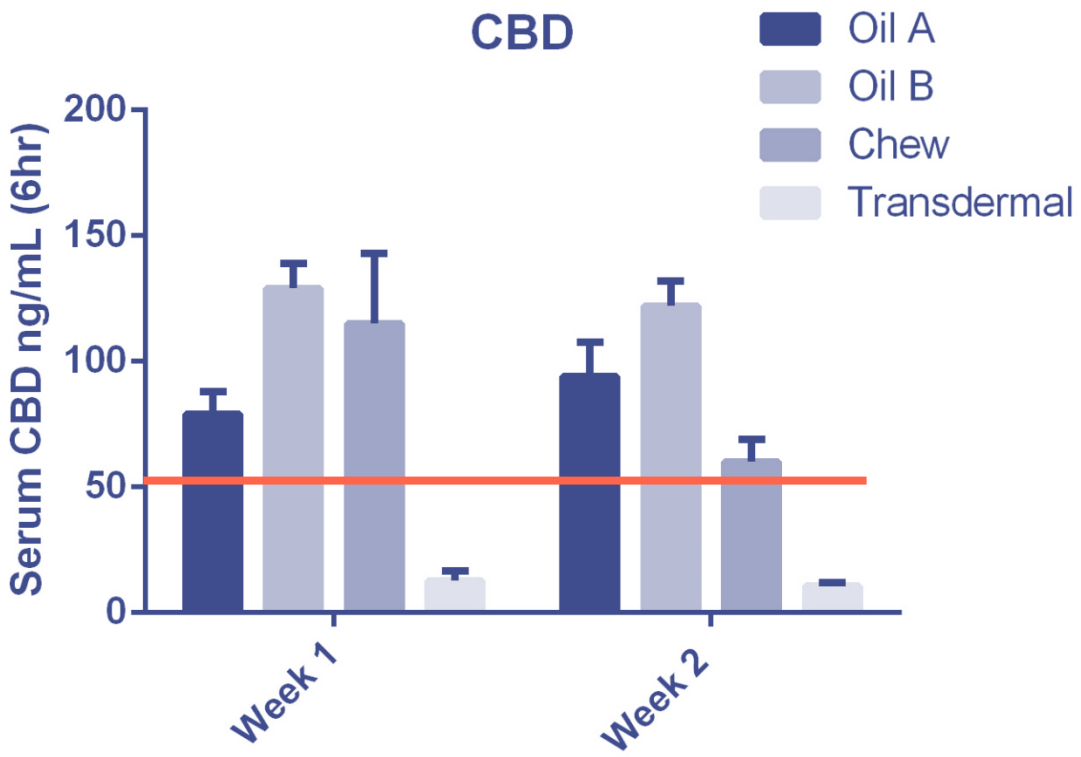
Soft Chew

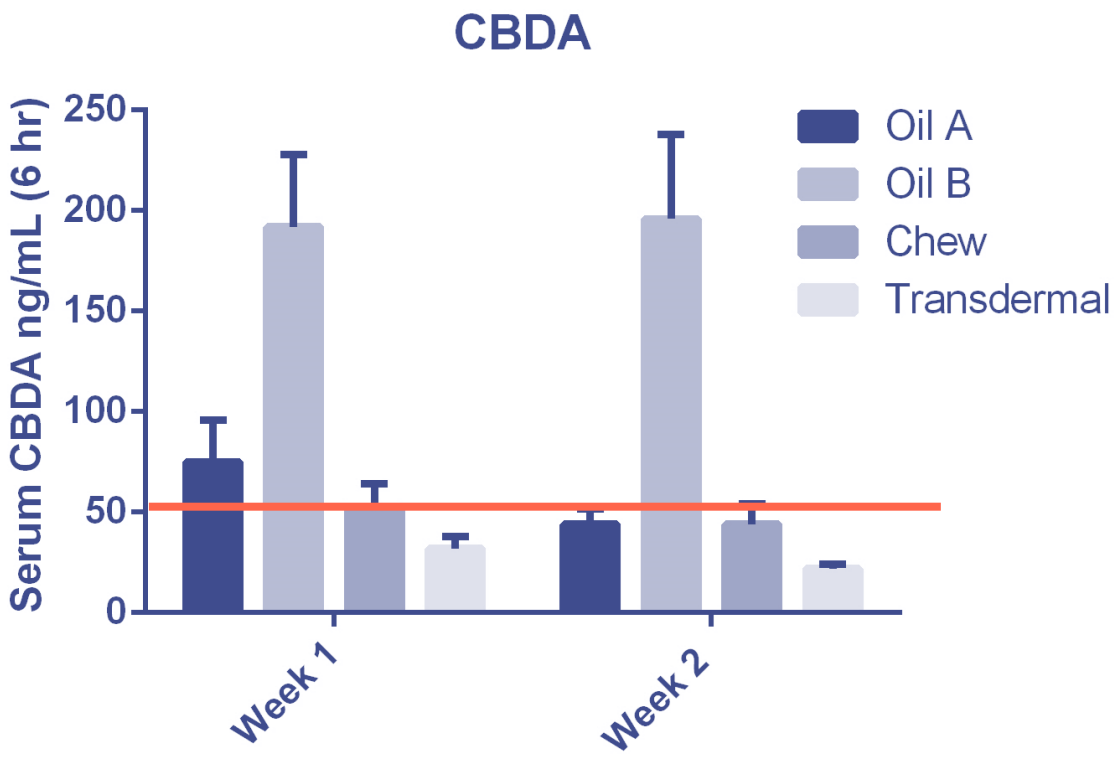


ElleVet SCIENCES

Cannabidiols – 2 weeks

2 Weeks – mid point after last dose (6hrs)

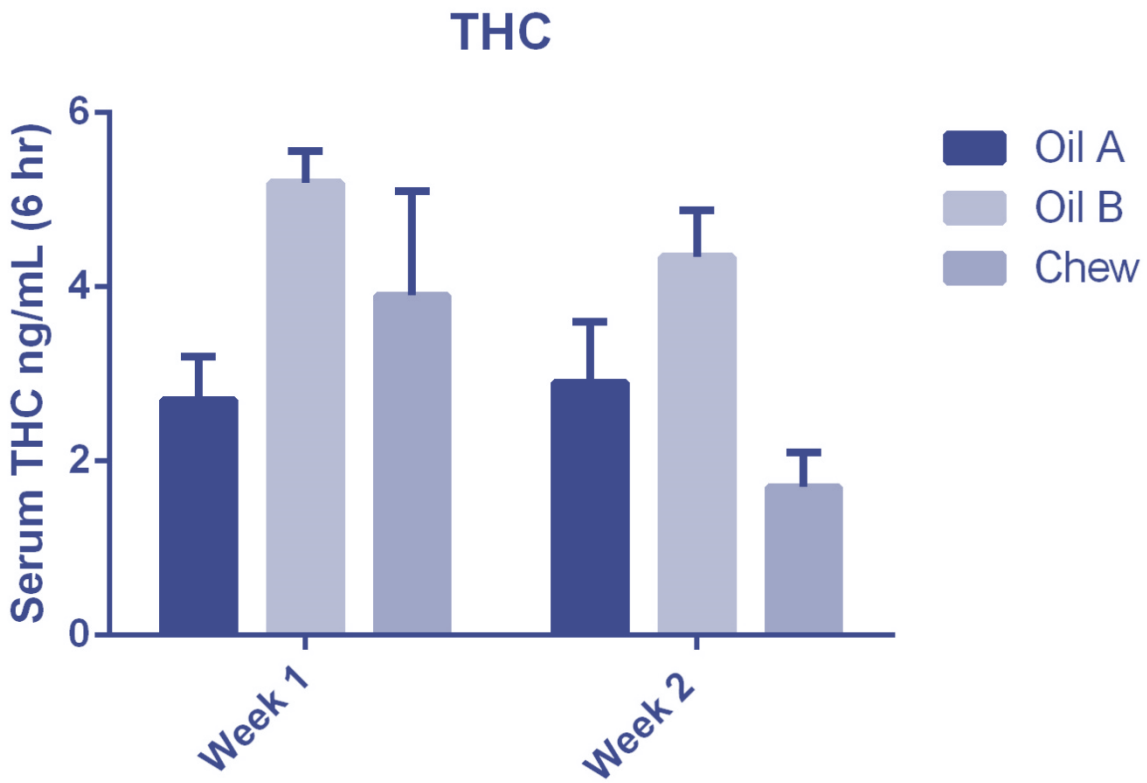


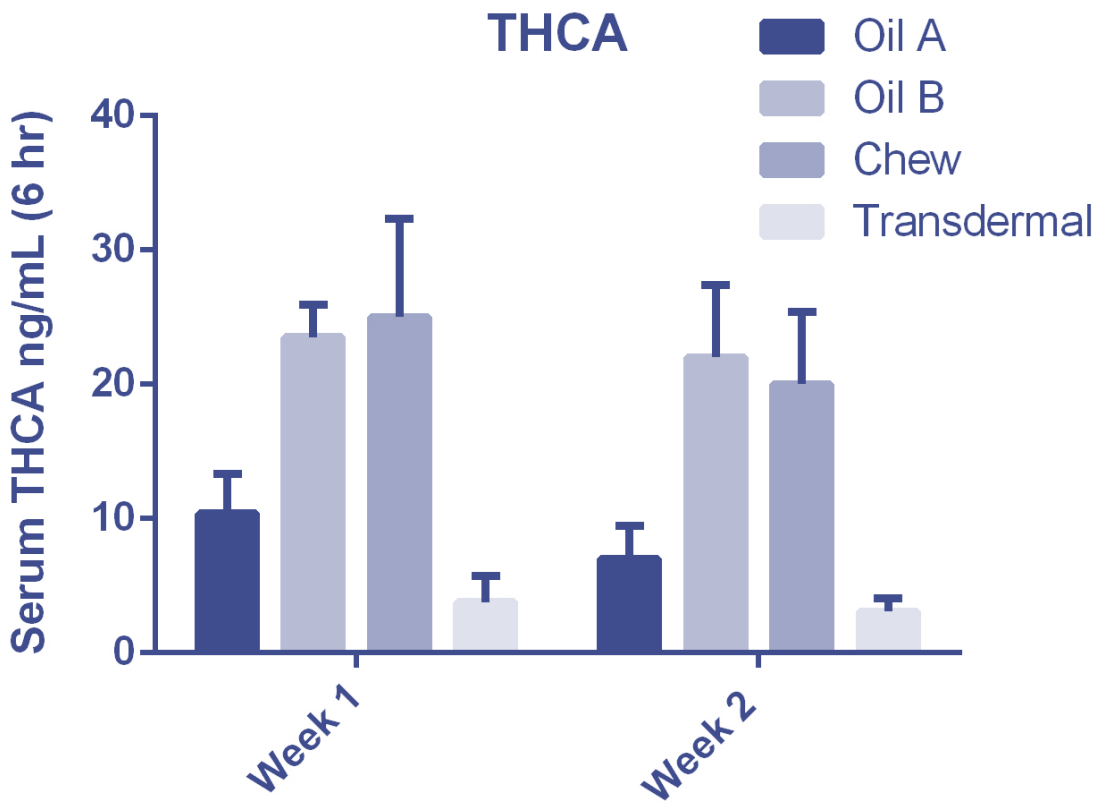


ElleVet SCIENCES

THC's – 2 weeks

2 Weeks – mid point after last dose (6hrs)

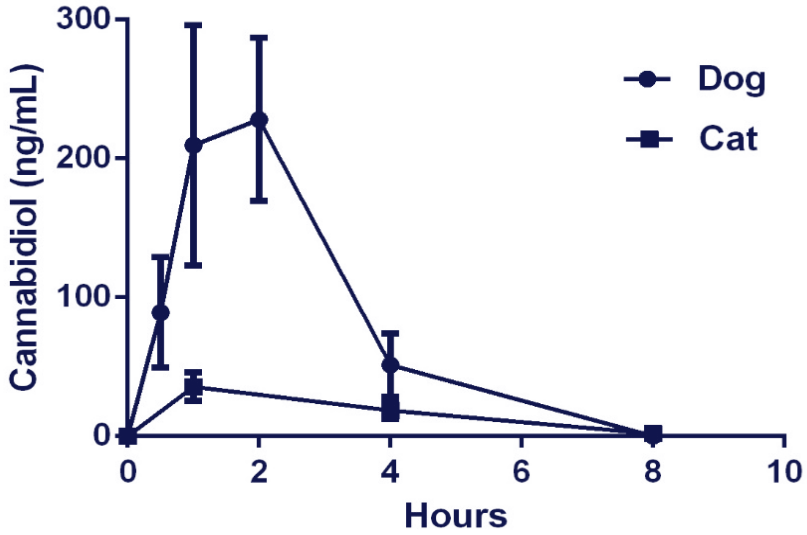




ElleVet SCIENCES

New Ellevet Cat PK Study – palatable paste!

- Biggest problem with cat complete spectrum products are palatability
- Oil tends to cause hypersalivation and head shaking
- We do not want to produce negative owner interactions
- Paste candidate was provided at approximately 3.2 mg/kg
  (1.6 mg CBD/CBDA/kg) to 8 cats at CRO
- Assessed daily PE and tolerance
- All cats took paste willingly.
- CBC and Chemistry evaluation prior to treatment and 1 week - No differences observed.
- 24 hour PK and week 1 steady state assessed



ElleVet SCIENCES

24 hour Pharmacokinetics of a Cat Paste

Serum Cannabinoid 24 h and 1 Week Steady State Pharmacokinetic Assessment in Cats Using a CBD/CBDA Rich Hemp Paste

*Tongxin Wang[1], Alex Zakharov[2], Beatriz Gomez[2], Alex Lyubimov[2], Nathalie L. Trottier[1], Wayne S. Schwark[3] and Joseph J. Wakshlag[4]**

	Fish Oil (1 mg/kg CBD)	Paste (1.6 mg/kg CBD)
Cmax (ng/mL)	43	282
AUC (ng-h/mL)	164	909
T1/2 el (hr)	1.5	2.0

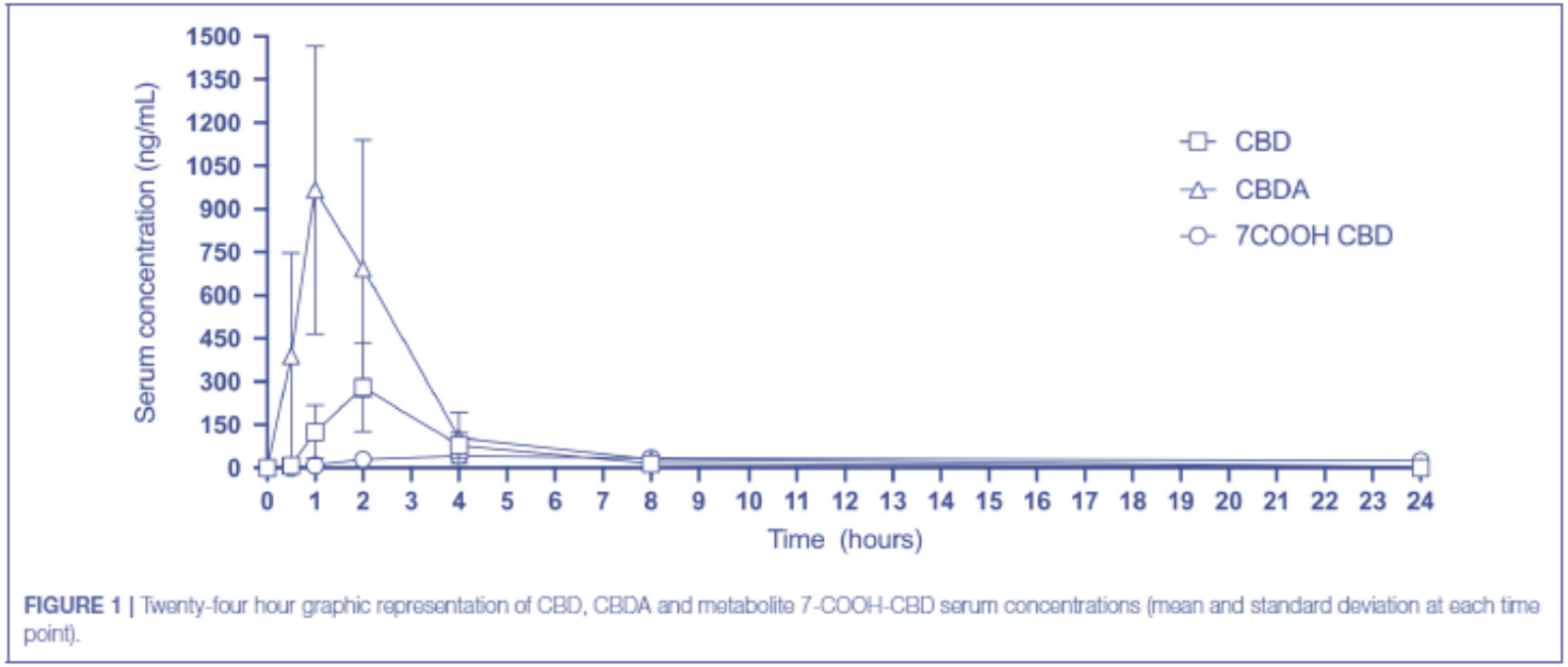


FIGURE 1 | Twenty-four hour graphic representation of CBD, CBDA and metabolite 7-COOH-CBD serum concentrations (mean and standard deviation at each time point).

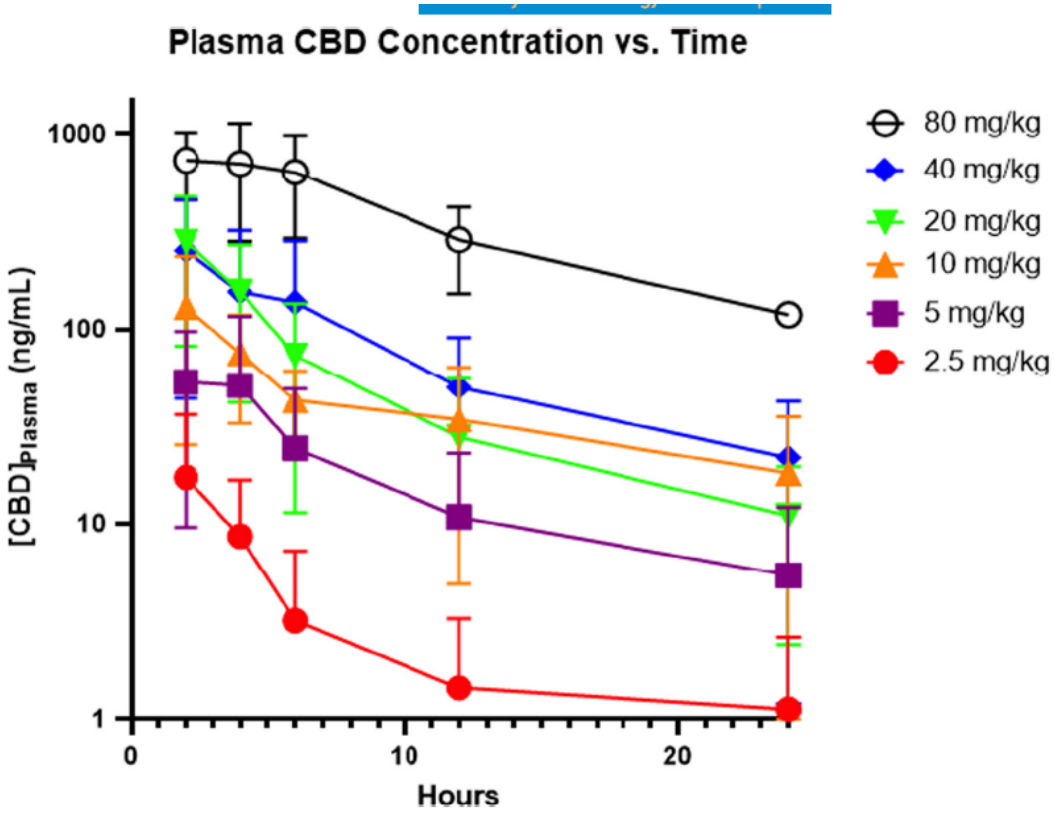
ElleVet SCIENCES

Cats – Oils vs Paste! Whole vs isolate?

	Fish Oil (1 mg/kg CBD)	Paste (1.6 mg/kg CBD)	Sunflower oil (2.5 mg/kg CBD)
Cmax (ng/mL)	43	282	18
AUC (ng-h/mL)	164	909	83
T1/2 el (hr)	1.5	2.0	2.0

Pharmacokinetics of escalating single-dose administration of cannabidiol to cats

Aaron J. Rozental | Daniel L. Gustafson | Breonna R. Kusick | Lisa R. Bartner | Stephanie Cruz Castro | Stephanie McGrath



Time 0 and the Time 24 evaluations. Creatine kinase activity was also consistently elevated at the 24-h blood draw compared to Time 0.

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Steady State PK – acids vs neutrals?

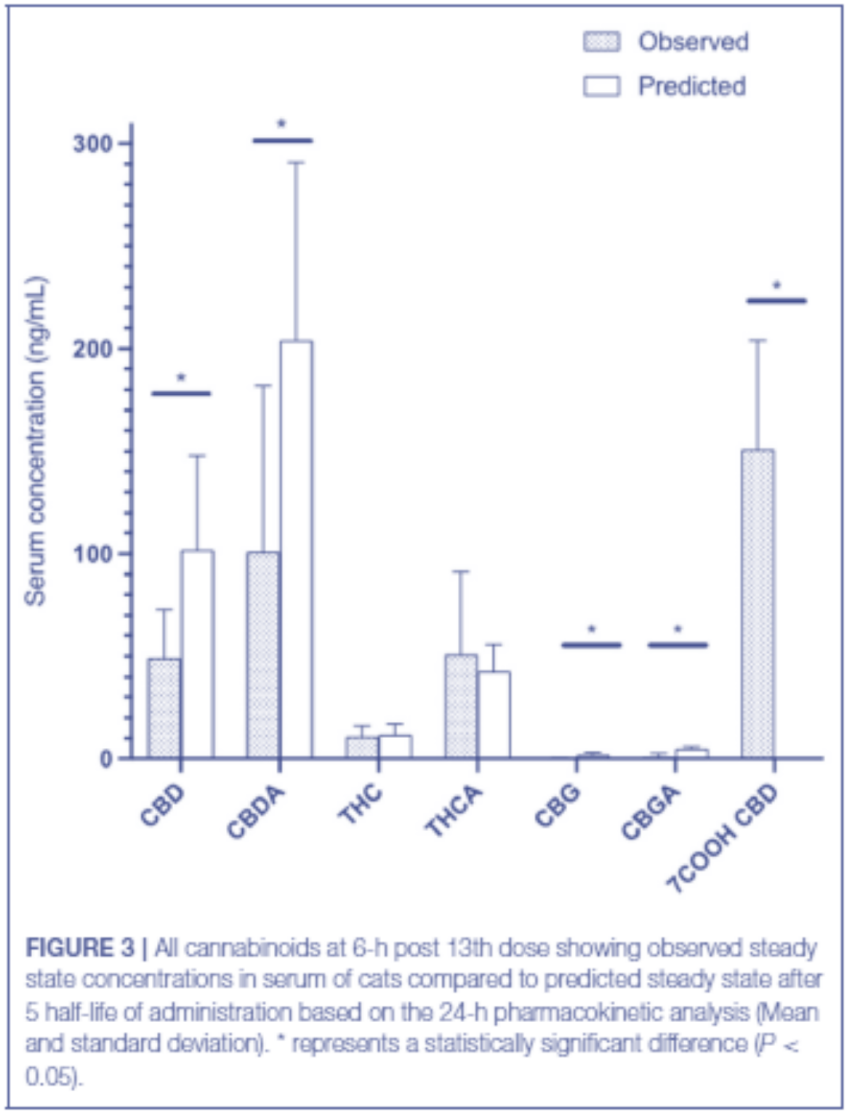
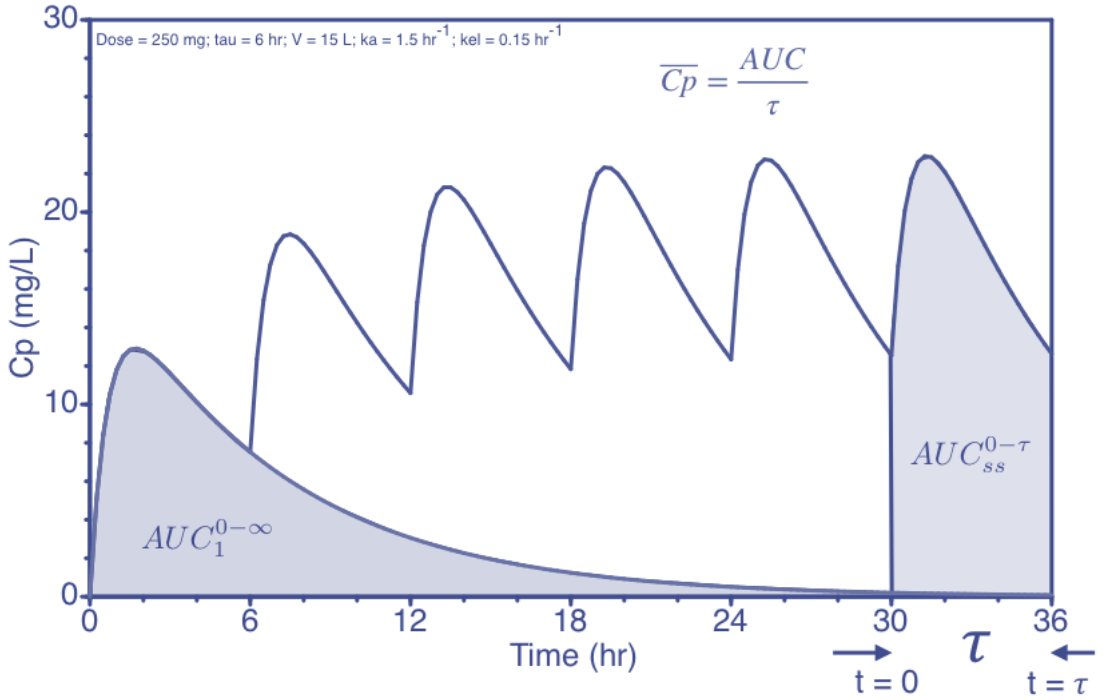


FIGURE 3 | All cannabinoids at 6-h post 13th dose showing observed steady state concentrations in serum of cats compared to predicted steady state after 5 half-life of administration based on the 24-h pharmacokinetic analysis (Mean and standard deviation). * represents a statistically significant difference ($P < 0.05$).



Cannabinoid	Predicted	Observed
CBD (ng/mL)	102	49*
CBDA (ng/mL)	205	102*

* Significantly different

Horse 24 hr CBD PK:

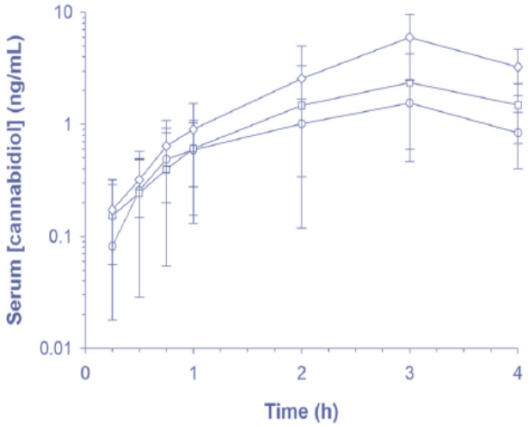
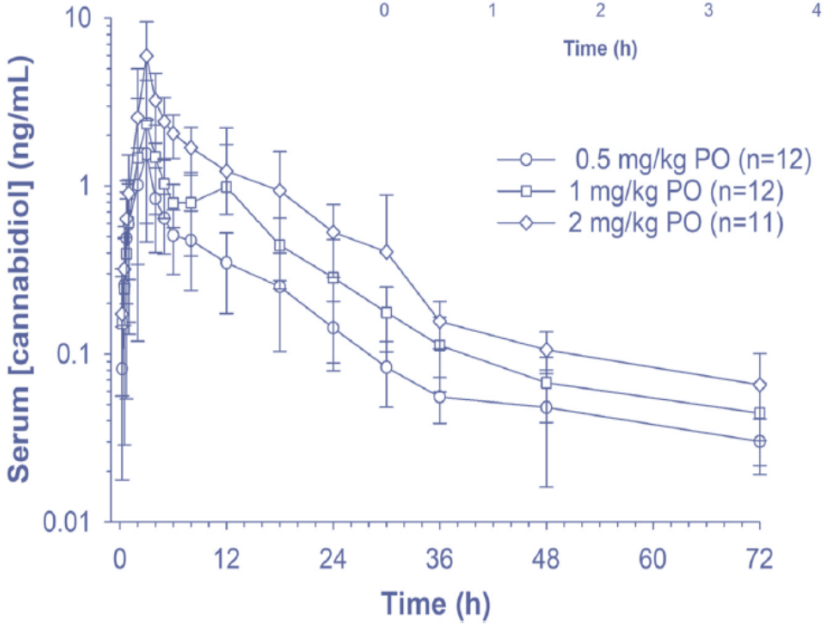


FIGURE 2 Average ± SD serum concentrations of cannabidiol with respect to time after a single oral administration of CBD (0.5, 1, and 2 mg/kg) to 12 horses



Received: 4 January 2021 | Revised: 9 March 2021 | Accepted: 11 March 2021
DOI: 10.1002/dta.3028

RESEARCH ARTICLE

WILEY

Pharmacokinetics and effects on arachidonic acid metabolism of low doses of cannabidiol following oral administration to horses

Declan Ryan[1] | Dan S. McKemie[1] | Philip H. Kass[3] | Birgit Puschner[4] | Heather K. Knych[1,2]

Parameters	Dose groups		
	0.5 mg/kg (*n* = 12)	1.0 mg/kg (*n* = 12)	2.0 mg/kg (*n* = 11)
C_{max} ng/ml	1.69 ± 0.830[b,c]	3.22 ± 2.18[a,c]	6.14 ± 3.52[a,b]
T_{max} (hr)	2.81 ± 0.984	4.75 ± 3.77	3.18 ± 0.982
$Lambda_z$(1/hr)	0.072 ± 0.024	0.073 ± 0.023	0.078 ± 0.027
HL $Lambda_z$ (hr)	10.7 ± 3.61	10.6 ± 3.84	9.88 ± 3.53
$AUC_{0\text{-}inf}$ (hr*ng ml)	13.2 ± 4.73[b,c]	23.5 ± 7.47[a,c]	44.2 ± 16.2[a,b]
AUC extrap (%)	19.6 ± 10.7[b,c]	9.79 ± 5.65[a,c]	5.45 ± 4.66[a,b]
CL/F (ml/min/kg)	732.2 ± 321.9	761.6 ± 190.1	754.1 ± 240.9

ElleVet Horse Studies:

University of Florida

- 2 mg/kg and 8 mg/kg - Ellevet full spectrum oil with 24 hr PK
- Assess GI motility after application as well – barium ball passage with radiographic assessment – ALL NORMAL

Cornell University

- 7 older horses – 6 week cross over of CBDA vs CBD (1 mg/kg) – BID for 6 weeks
- CBC/Chemistry
- Liver biopsy before and after – ALL NORMAL
- Serum PK and biweekly peak trough assessment of cannabinoids

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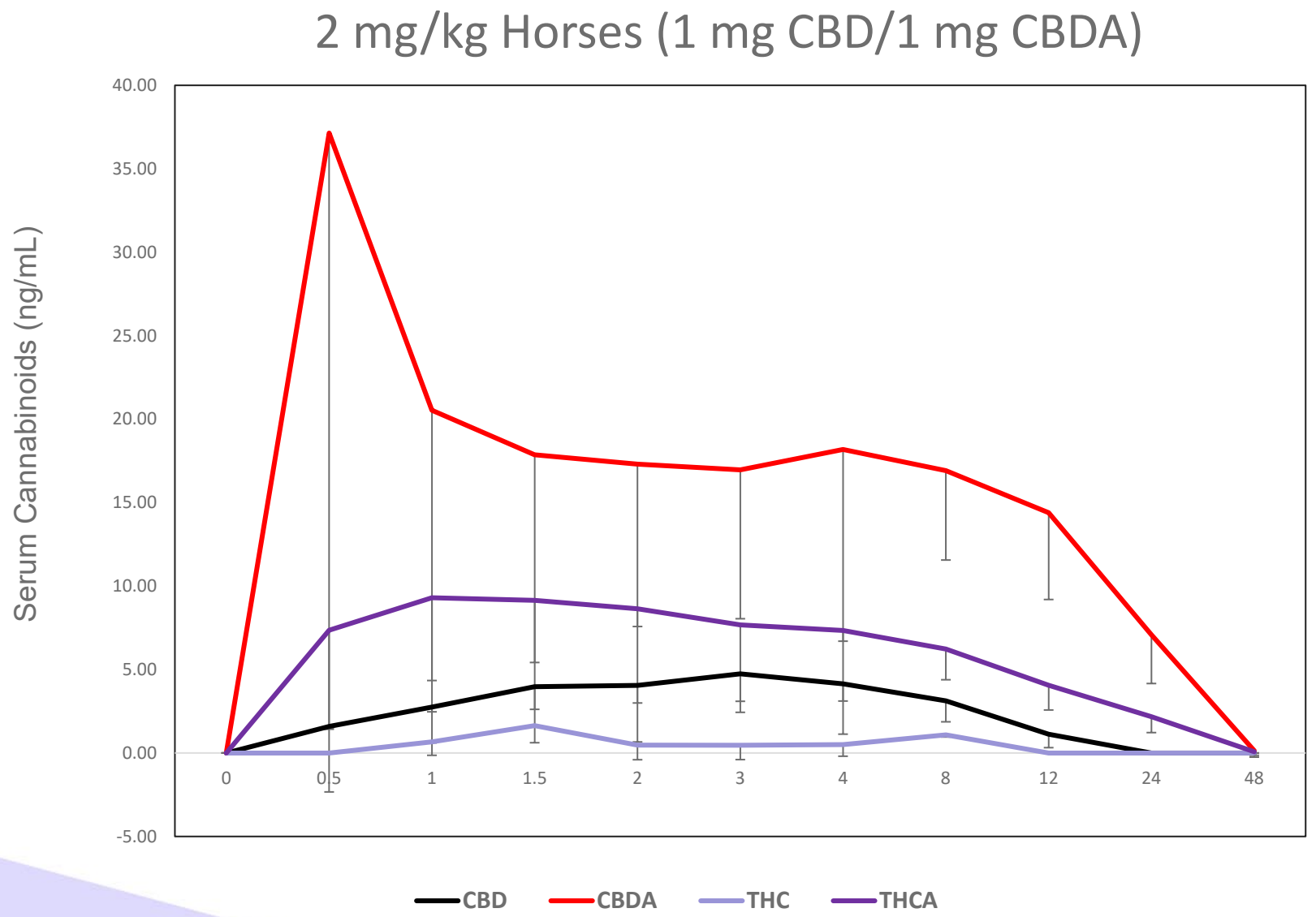
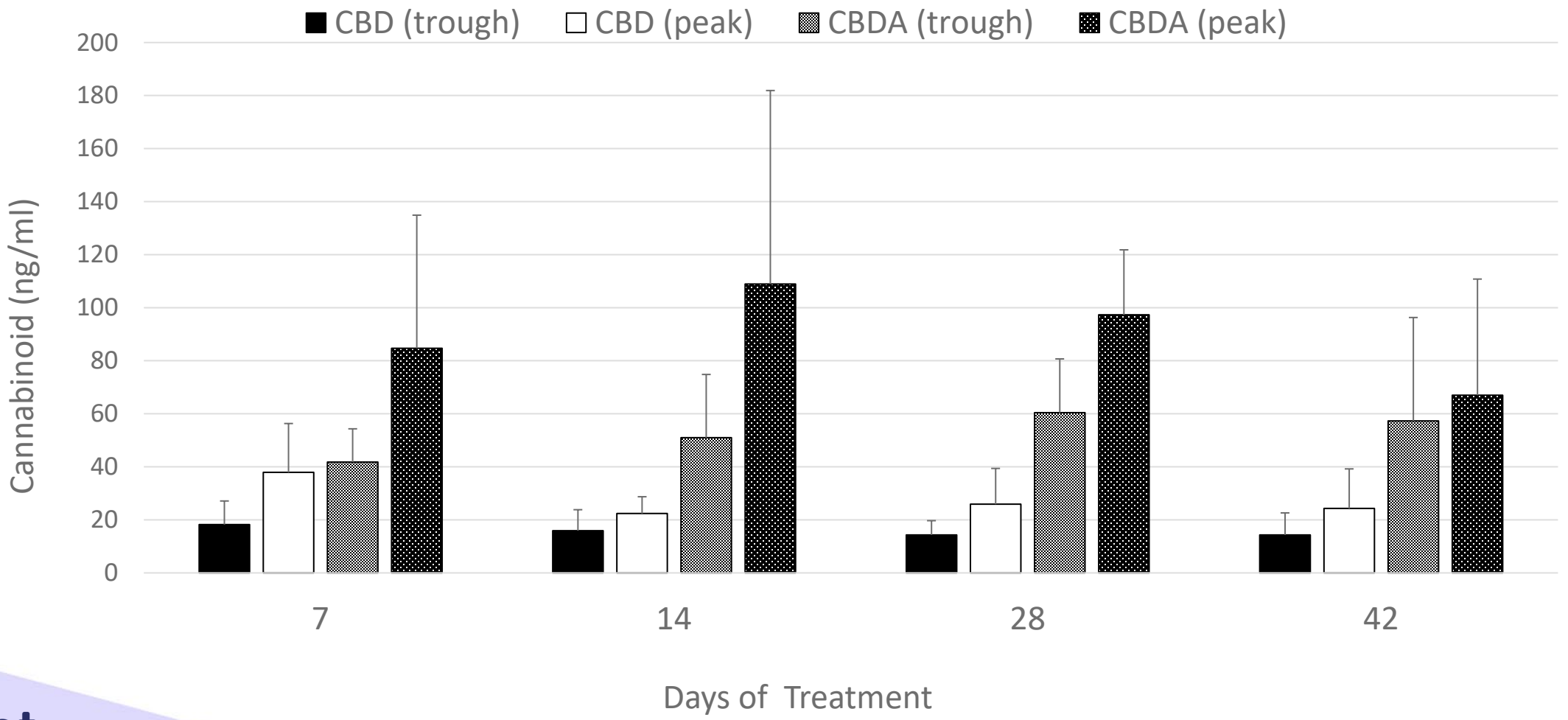
Preliminary Look CBD and Other Cannabinoids:



Horse Steady State PK of CBD and CBDA – Peak and Trough



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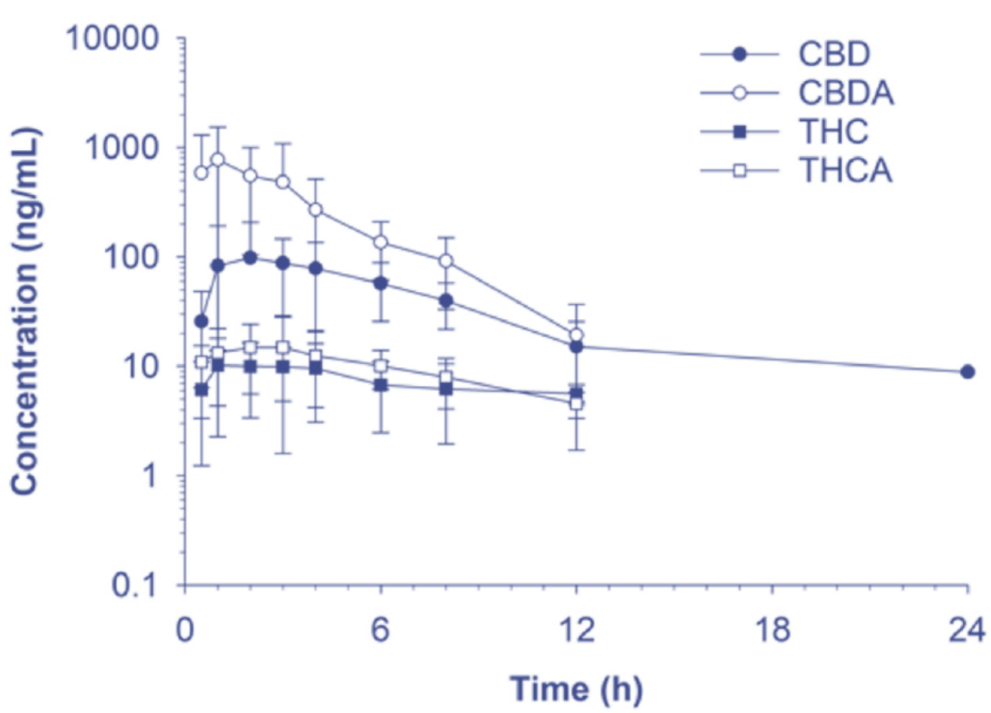
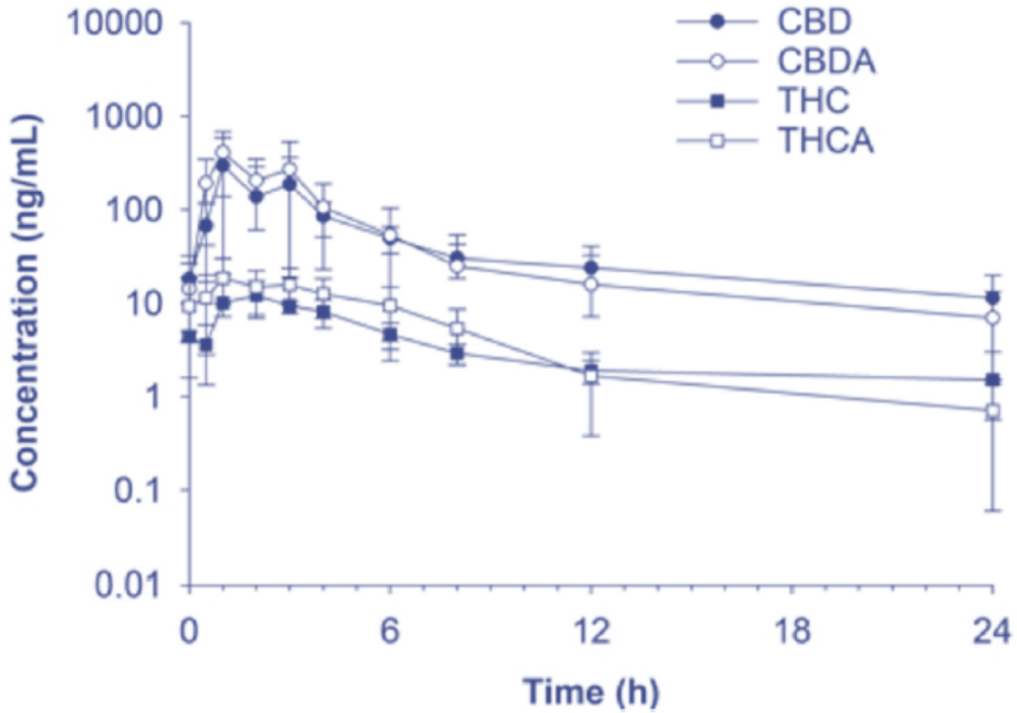
CBD/CBDA in Parrots – 30 mg/kg CBD/30 mg/kg CBDA!

Pharmacokinetics of cannabinoids and metabolites in orange-winged Amazon parrots (*Amazona amazonica*) following oral administration of single and multiple doses of a hemp extract

24 hour PK → **1 week Treatment** → **24 hour PK**

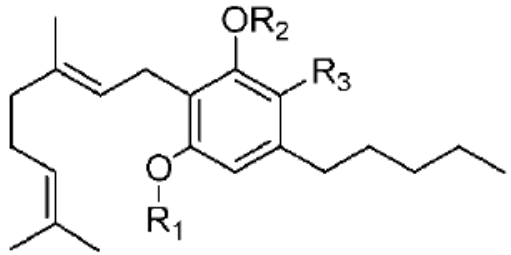




What about other Cannabinoids? CBG/CBGA?

Initial Cannabinoid synthesized in Cannabis

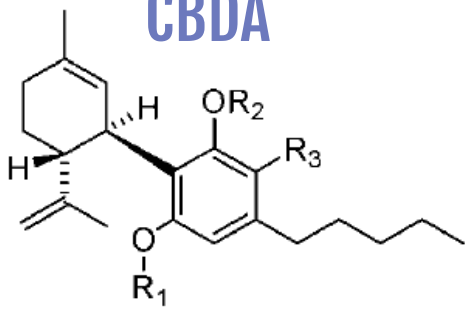
CBGA



Plant CBDA synthase activity

Primary Cannabinoid found in Hemp cultivars

CBDA



Heat processing or heat drying

CBG

CBD

ElleVet SCIENCES

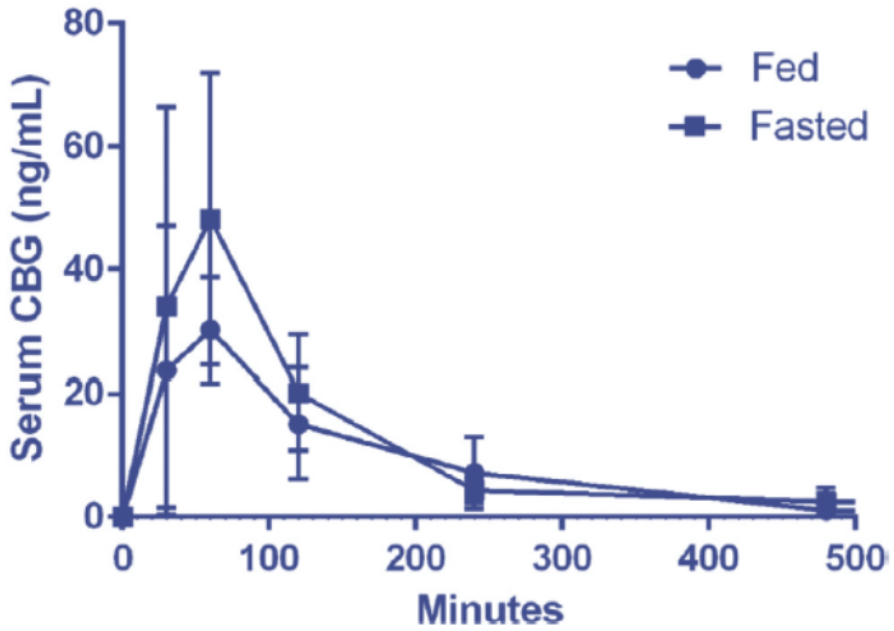
24 hr PK fed and fasted CBG/CBGA –1 mg/kg of each

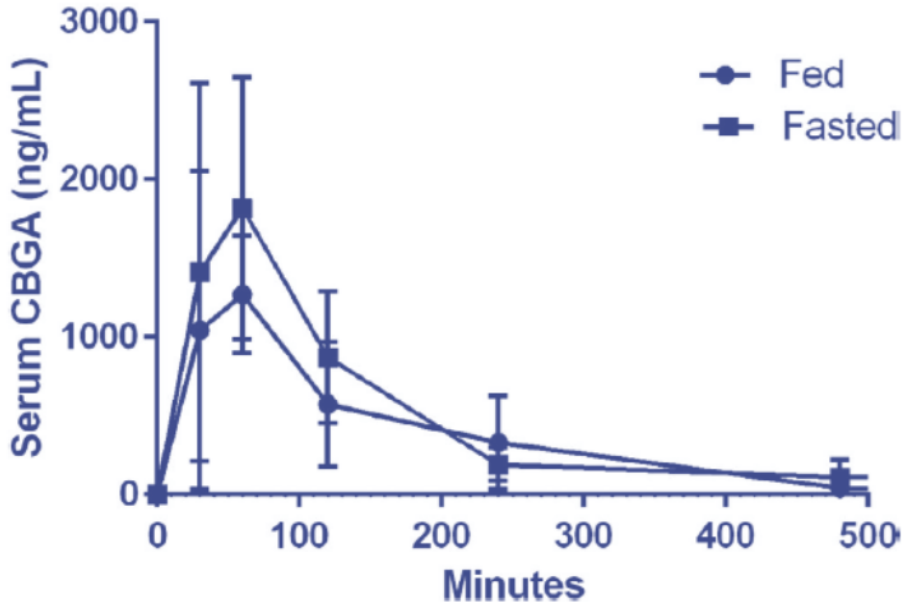
DOI: 10.1111/jvp.13048

ORIGINAL ARTICLE

Journal of Veterinary Pharmacology and Therapeutics WILEY

Single dose and chronic oral administration of cannabigerol and cannabigerolic acid-rich hemp extract in fed and fasted dogs: Physiological effect and pharmacokinetic evaluation





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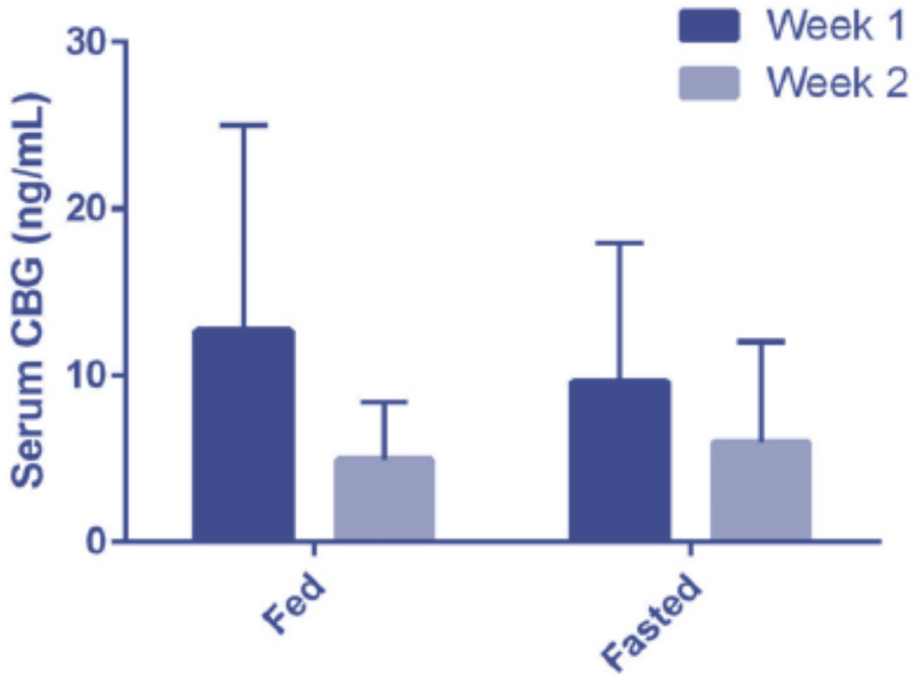
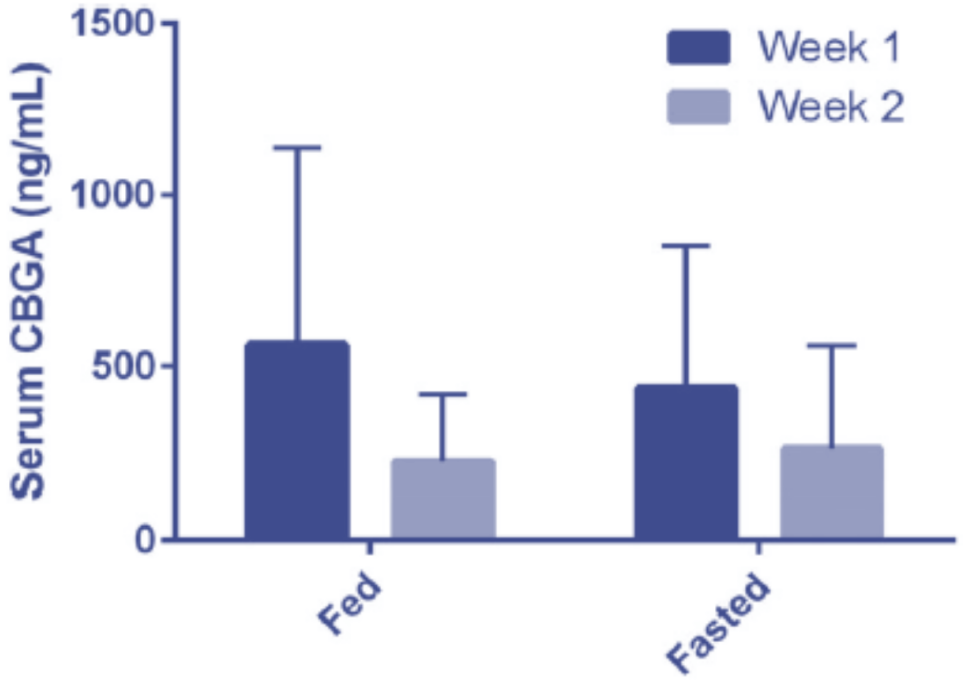
1 and 2 week steady state CBG/CBGA





ElleVet SCIENCES

A lot of companies and a lot of cannabinoids!

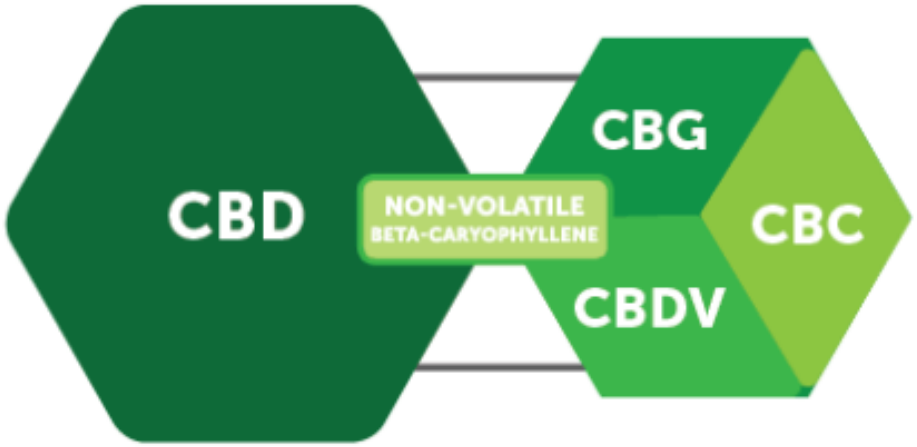
COMFORT (HIP AND JOINT)

Form: Chew

C2P Formula: P/$\frac{G}{D}$

Indications: Muscle Pain, Joint Pain, Mobility, Arthritis, Immune Support

Isolated Cannabinoids: CBG, CBD



NO THC

Ask them why?

Where is the PK data to support your blend?

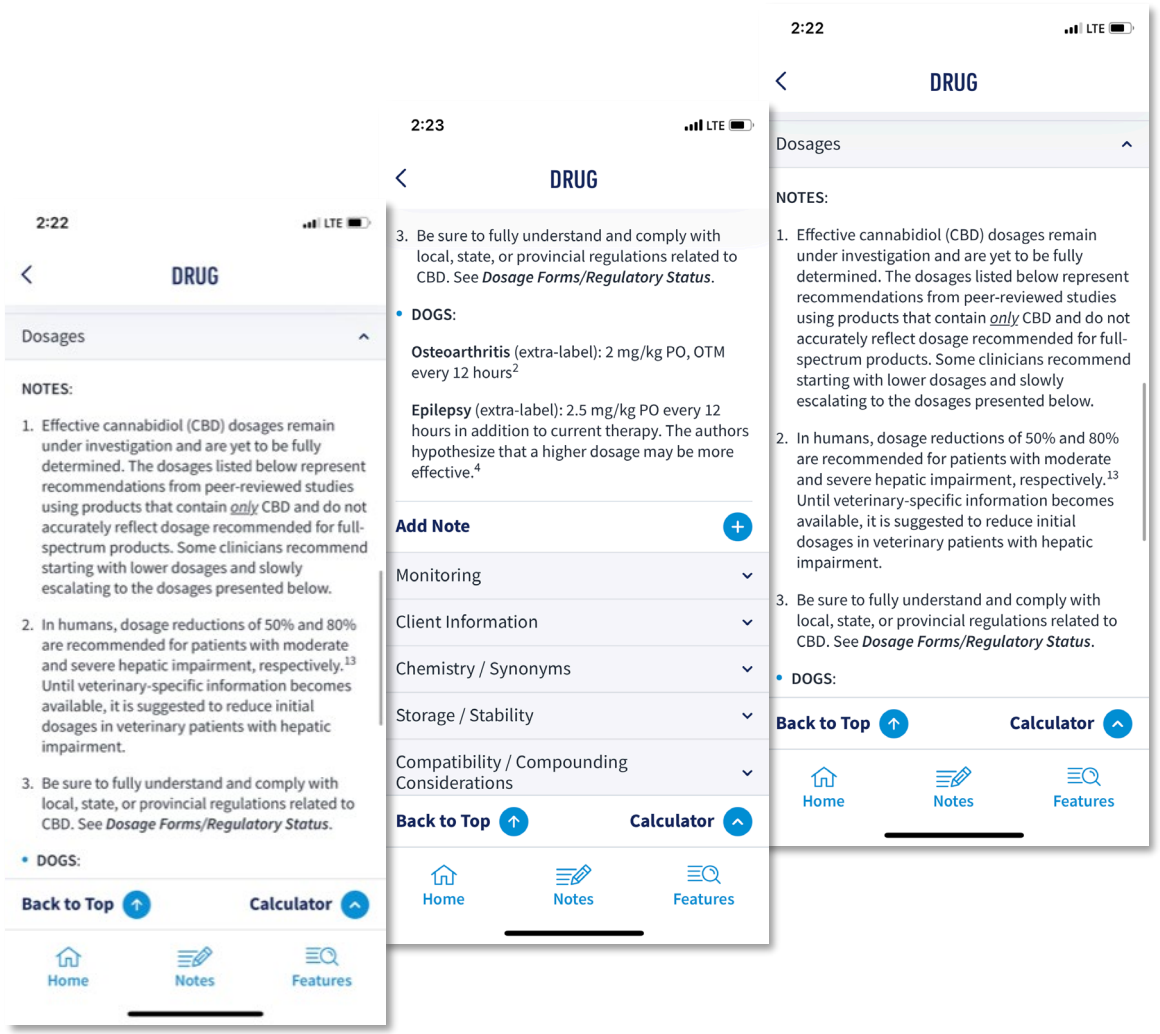
ElleVet SCIENCES

AAVSB – Pharmacokinetics, Safety, NASC, Efficacy

NASC Label	Safety Study	RCT Canine OA	Positive Results
• ElleVet ✓	• ElleVet ✓	• ElleVet ✓	• ElleVet ✓
• ~~ABSC~~	• ~~ABSC~~	• ABSC ✓	• ~~ABSC~~
• ~~Holistapet~~	• ~~Holistapet~~	• ~~Holistapet~~	• ~~Holistapet~~
• ~~Chroniquin~~	• ~~Chroniquin~~	• ~~Chroniquin~~	• ~~Chroniquin~~
• Charlotte's Web ✓	• ~~Charlotte's Web~~	• ~~Charlotte's Web~~	• ~~Charlotte's Web~~
• HempRx✓	• ~~Hemp Rx~~	• ~~Hemp Rx~~	• ~~Hemp Rx~~

ElleVet SCIENCES

CBD is now also integrated in Plumb's



CBD use!

- 2 mg/kg in 30 kg Labrador BID – 60 mg BID
- Likely to need over 25 mg/ml solution for appropriate dosing without excessive oil or powder.
- 20 mg/ml – 3 ml BID; 60 mg/ml – 1 ml BID

ElleVet SCIENCES

Reviews of Interest

AJVR Currents in One Health
Leading at the intersection of animal, human, and environmental health
AVMA

A One Health perspective on comparative cannabidiol and cannabidiolic acid pharmacokinetics and biotransformation in humans and domestic animals

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ABSTRACT

The goal of pharmacokinetic (PK) studies is to provide a basis for appropriate dosing regimens with novel therapeutic agents. With a knowledge of the desired serum concentration for optimum pharmacological effect, the amount and rate of drug administration can be tailored to maintain that concentration based on the 24-hour PK modeling (eg, every 24 hours, every 12 hours) to achieve therapeutic ranges. This dosing and PK information are tailored to maintain that concentration. Typically, these optimum serum concentrations pertain across species. Single-dose PK modeling provides fundamental parameters to suggest dosing regimes. Multiple-dose PK studies provide information on steady-state serum levels to assure that desired therapeutic levels are maintained during chronic administration. Clinical trials using dosing suggested by these PK determinations provide proof that the compound is producing the desired therapeutic effect. A number of PK studies with cannabinoids in humans and domestic animals have been conducted with the goal of determining appropriate clinical use with these plant-derived products. The following review will focus on the PK of cannabidiol (CBD) and the lesser-known precursor of CBD, cannabidiolic acid (CBDA). Although Δ9-tetrahydrocannabinol (THC) has profound pharmacological effects and may be present at variable and potentially violative concentrations in hemp products, PK studies with THC will not be a major consideration. Because, in domestic animals, hemp-CBD products are usually administered orally, that route will be a focus. When available, PK results with CBD administered by other routes will be summarized. In addition, the metabolism of CBD across species appears to be different in carnivorous species compared with omnivorous/herbivorous species (including humans) based on current information, and the preliminary information related to this will be explained with the therapeutic implication being addressed in Currents in One Health by Ukai et al, *JAVMA*, May 2023.

PK Studies with CBD in Dogs

In domestic animals to the present, the greatest number of pharmacokinetic (PK) studies with hemp cannabidiol (CBD) have been conducted in dogs. Indeed, the correlation between CBD serum levels and clinical effectiveness in conditions such as seizure disorders and osteoarthritis is established in canine patients.[1,2] Initial PK studies with CBD in dogs showed an extremely low bioavailability (0% to 19%) with some dogs showing no serum levels after oral administration.[3] This may be due to first-pass hepatic metabolism or the type of formulation utilized (powder in a gelatin capsule).[4]

Bartner et al studied the PK of oral forms (microencapsulated oil beads, CBD-infused oil) and a topical preparation (CBD-infused transdermal cream) in dogs.[5] Oral dosage levels of CBD were 10 and 20 mg/kg, which is higher than that used in subsequent oral studies in dogs. The oil preparations resulted in a higher maximal serum concentration (C_{max}) and area under the curve (AUC; see **Table 1**) with both oral doses than in the report cited above.[3] As a follow-up, the drugs were administered in similar doses chronically (6 weeks) to determine adverse effects. The C_{max} levels after the 6-week period were similar to that after a single dose, indicating that there were no alterations in elimination rate with chronic administration.

Gamble et al found a dose-dependent absorption of CBD in a CBD/CBDA-rich hemp mixture. Oral administration of the mixture in oil (1 and 4 mg/kg CBD, as the 2 mg/kg and 8 mg/kg dose contained an equal amount of cannabidiolic acid [CBDA], which was not assessed pharmacokinetically) resulted in median C_{max} levels of 102 and 591 ng/mL and AUCs of 376 and 2,658 ng·h/mL.[1] This group subsequently reported a PK study with oral 1 mg/kg CBD in a CBD/CBDA soft chew preparation and found substantial CBD absorption (C_{max} of 301 ng/mL and

JAVMA AVMA

Key quality control aspects about cannabinoid-rich hemp products that a veterinarian needs to know: a practitioner's guide

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[2]Ellevet Sciences, South Portland, ME
[3]Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY

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ABSTRACT

There is considerable confusion in the veterinary profession surrounding the rise in hemp cannabidiol-based animal products and what veterinarians should know before discussing these products with clients. There is emerging evidence for the potential use in case management across many veterinary indications; however, the cannabinoid concentrations and whether these are isolated cannabinoids or whole hemp extracts is difficult to elucidate, even from the published papers. Much like any extract from a plant, there are multiple considerations including quality control, pharmacokinetics in the intended species, microbiological and chemical contamination, and product consistency—all aspects that should be considered before a conversation can begin with a client. The aim of this review is to help practitioners make informed decisions and better facilitate discussions with clients for companion animals kept as pets. This review will not address food animal issues, as established withholding times have yet to be fully researched.

An Overview of Hemp-derived *Cannabis* and Cannabinoids

The main cultivars of hemp include *Cannabis sativa* and *Cannabis indica* strains, and significant cross breeding across the industry often makes distinguishing *Cannabis* species difficult. The *Cannabis* plant can produce over 100 different cannabinoids. All cannabinoids are derived from an initial cannabinoid called cannabigerolic acid (CBGA). In general, depending on the genetics of the plant and various synthase activities, CBGA will be endogenously metabolized into other cannabinoids; however, *Cannabis* breeding and hybridization of plants has allowed for development of strains that primarily make CBGA through elimination of synthases that form other cannabinoids. The 2 cannabinoids that predominate are tetrahydrocannabinolic acid (THCA) in marijuana and cannabidiolic acid (CBDA) in hemp. There are some plants that make larger quantities of cannabichromenic acid as well **(Figure 1)**.[1] During processing and storage, there is decarboxylation of the acidic forms into the neutral forms, particularly if exposed to light, oxygen, and heat.[2] This decarboxylation will lead to production of the neutral cannabinoids, Δ9-tetrahydrocannabinol (THC) or cannabidiol (CBD). Additionally, any residual THC can be isomerized to Δ8-THC or cannabinol, which are not native to the plant but may have potential pharmacological properties.[3] Many of these cannabinoids are routinely tested for by analytic laboratories, the results of which should be available for practitioners to view in a certificate of analysis (COA) before recommending a product to their clients, and this testing laboratory should be certified for cannabinoid analysis (see Current Status of Testing below). Most importantly, most hemp products will have residual THCs consistent with a hemp extract (< 0.3%) rather than marijuana, which will be higher. Δ9-THC is the primary cannabinoid that should be avoided as THCA is nonpsychotropic, yet decarboxylation of THCA can occur over time or with heating, leading to Δ9-THC formation. In addition, processing of hemp may lead to exo-THC or Δ8-THC formation, which, although less psychotropic, can be found in analyses in small amounts; therefore, we recommend that veterinarians ensure that the total THCs (including THCA, THC, exo-THC, and Δ8-THC) is no more than 0.3% (eg, an oil or chew should be < 3 mg/mL or g), which is often the case for veterinary hemp CBD products.[4] What is important to understand is that many reports will say that THC derivatives are not detectable, yet if the lower limit of detection is 1 mg/mL or g, it would be deemed free of THC; hence, the lower limit of detection should be

JAVMA Currents in One Health
Leading at the intersection of animal, human, and environmental health
AVMA

The clinical use of cannabidiol and cannabidiolic acid–rich hemp in veterinary medicine and lessons from human medicine

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ABSTRACT

The endocannabinoid system (ECS) is an integral neuromodulatory system involved in neuronal development, synaptic plasticity, and homeostasis regarding immunity, as well as brain and other physiological functions such as anxiety, pain, metabolic regulation, and bone growth. *Cannabis* is a plant that contains exogenous cannabinoids, which have the potential for profound interplay within the ECS as enzymatic inhibitors or receptor-mediated interactions. Activation of cannabinoid receptors leads to various intracellular signaling processes that are involved in cellular functions, but those interactions are diverse due to different affinities of each cannabinoid with relevant receptors. Among the exogenous cannabinoids, cannabidiol (CBD) has drawn attention due to its potential anticancer, antiangiogenic, anti-inflammatory, and antiseizure properties using in vitro and in vivo models. Although scientific evidence is limited in dogs, there appears to be cautious optimism regarding the utilization of CBD in conjunction with other therapeutics for a range of disorders. This review will primarily focus on current scientific research on the efficacy of CBD on seizure, anxiety, osteoarthritis, and atopic dermatitis, following a brief discussion of endo- and exogenous cannabinoids, ECS, their molecular mechanism, and potential side effects in veterinary medicine. Cannabinoid pharmacology and pharmacokinetics will be addressed in the companion Currents in One Health by Schwark and Wakshlag, *AJVR*, May 2023.

The Endocannabinoid System: Beyond Cannabinoid Receptors

Endocannabinoids (endogenous cannabinoids [ECs]), endocannabinoid receptors, several other receptors activated by ECs, and the enzymes that synthesize and degrade ECs constitute the endocannabinoid system (ECS).[1] The ECS is an integral neuromodulatory system that is involved in neuronal development, synaptic plasticity, and homeostasis regarding immunity as well as brain and other physiological functions.[1] Endocannabinoids primarily refer to 2-arachidonoyl glycerol and arachidonoyl ethanolamide (anandamide), both of which have been well studied.[1] In the CNS, ECs are secreted through the postsynaptic membrane of neurons and act on presynaptic receptors—endocannabinoid receptors 1 and 2 (CB1 and CB2 receptors)—causing hyperpolarization following increasing K^+ cell influx.[2] This leads to inhibitory neurotransmitter modulation that can facilitate diverse biological and physiological processes such as anxiety, pain, metabolic regulation, immunity, and bone growth.[3] In addition, ECs have different affinities to CB receptors, and their half-life is short due to the rapid metabolism by enzymes (fatty acid amide hydrolase and monoacylglycerol lipase).[4]

CB1 receptors are expressed primarily on cells in the CNS.[5] CB2 receptors are identified mainly on leukocytes but also on neurons and, to a small degree, glial cells, especially during pathological conditions such as degeneration, inflammation, and anxiety, although its level of expression on neurons in the brain is lower than that of CB1 receptors.[6,7] CB2 receptors have been shown to play an essential role in the anti-inflammatory and immunomodulatory properties of cannabinoids and can contribute to induction of apoptosis, which contributes to the immunosuppression effects of cannabinoids.[7-9] Interaction between ECS and cannabinoids will be discussed in more detail in each clinical application section below.

Plant-derived Cannabinoids

As described, the ECS has tremendous implications in neurological homeostasis, and *Cannabis sativa*– or

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Questions?

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