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ORIGINAL ARTICLE

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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Abstract

The use of cannabinoids in veterinary medicine has been increasing exponentially recently and there is little information regarding the pharmacokinetics of cannabinoids except for cannabidiol (CBD) and tetrahydrocannabinol (THC), with even more sparse information related to their native acid forms found in cannabis. Cannabigerol (CBG) is the precursor molecule to cannabinoid formation in the cannabis plant which may have medicinal properties as well, yet there are no publications related to CBG or the native cannabigerolic acid (CBGA) in companion animal species. The aim of this study was to investigate similar dosing of CBG and CBGA from hemp plants that have been used for cannabidiol pharmacokinetic studies. Administration in the fed and fasted state was performed to better understand absorption and retention of these unique hemp-derived cannabinoids in dogs. Results suggest that when providing a hemp-derived CBG/CBGA formulation in equal quantities, CBGA is absorbed approximately 40-fold better than CBG regardless of being given to fed or fasted dogs. After twice daily dosing for two weeks at 2 mg/kg in the fasted and then fed state, no differences in the mean serum CBG (5 ng/ml) or CBGA (250 ng/ml) serum concentrations were observed between states. Importantly, physical examination, complete blood counts, and serum chemistry evaluations over the two weeks suggest no adverse events during this short-term dosing trial.

KEYWORDS
cannabigerol, cannabigerolic acid, dog, hemp, pharmacokinetics

1 | INTRODUCTION

Hemp-derived cannabinoids have recently become an area of interest in veterinary medicine. The phytocannabinoids from hemp are a group of over 60 compounds coming primarily from the medicinal plant *Cannabis sativa*. These compounds act on the endocannabinoid system, which is found in all animals, except insects. The endocannabinoid system is responsible for modulating neurologic function including anxiety and stress but also potentially, inflammation, pain, cardiopulmonary effects, metabolism, neoplastic cell growth, and antioxidant parameters (Silver, 2019).

The most widely studied cannabinoid compound, and the first to be isolated, Δ9-tetrahydrocannabinol (THC), has been shown to have many effects in humans. THC can cause side effects including static ataxia and urinary incontinence (Beardsley et al., 1987; Brutlag & Hommerding, 2018). Therefore, veterinary medicine has focused on other non-psychotropic cannabinoids such as cannabidiol (CBD) due to similar activities without the neurologic adverse events.

Pharmacokinetic studies evaluating dosing and safety of CBD in canine arthritic patients have been completed. A 6-week study using doses as high as 20 mg/kg show ample absorption of oral CBD in an oil base with minimal side effects (Bartner et al., 2018). A clinically effective dose of 2 mg/kg twice daily for osteoarthritis pain in dogs showed a significant rise in alkaline phosphatase activity on chemistry screens by 4 week of supplementation. Furthermore, no side effects such as ataxia, somnolence, or appetite changes were noted (Gamble et al., 2018).

Although THC and CBD have received most of the attention in the scientific community, it is important to realize there are other cannabinoids that can be isolated and utilized from the *C. sativa* plant. All *C. sativa* cannabinoids are synthesized from cannabigerolic acid making it the "mother" cannabinoid from which all other cannabinoids are synthesized, and has a carboxy-group in the cis- or trans-position from the alkyl tail of the molecule with cultivar dependent synthase activity inducing other cannabinoid synthesis in the plant. Cannabigerolic acid is the precursor molecule to both tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) (Fellermeier & Zenk, 1998). CBGA, found in lower concentration in *C. sativa*, was discovered around the same time as THCA and CBDA in 1964 (Gaoni & Mechoulam, 1964). CBGA becomes a decarboxylated compound, cannabigerol (CBG), during heat extraction. Regardless of the cannabinoid formed in the plant, this carboxylic acid is lost during most heat-driven extraction processes and this decarboxylated form is what is found in most nutraceutical products.

CBG has the potential for multiple effects because it acts upon a variety of receptors (Russo, 2011). CBG is a potent inhibitor of the transient receptor potential melastatin type 8 (TRPM8) receptor which is a non-selective cation channel that is activated by cold and cooling agents such as menthol (De Caro et al., 2019). This receptor has been linked with pain perception and is being studied extensively in human medicine as a target for inflammatory and neuropathic pain relief (Dai, 2016). CBG's effect on this receptor in mouse models with colorectal cancer has been shown to inhibit colorectal cancer cell proliferation and slow progression of this cancer type (Borrelli et al., 2014). This same mechanism has been studied with prostate cancer, bladder pain, and detrusor muscle activity (De Petrocellis et al., 2013; Mukerji et al., 2006). CBG's action on other transient receptor potential channels (TRP) receptors has demonstrated efficacy for gastrointestinal inflammation as well (De Petrocellis et al., 2012).

Little is known about CBGA or CBG in domestic species. However, in rodents, CBG has been proven to activate alpha (2)-adrenoceptors which are found in the central and peripheral nervous system and can provide analgesia, sedation, and muscle relaxation (Khan et al., 1999). CBG has an antidepressant action by antagonizing 5-HT1A receptors (Cascio et al., 2010). Finally, pre-clinical studies have been completed evaluating CBG's therapeutic effects for methicillin-resistant staphylococcus aureus infections (Appendino et al., 2008; Farha et al., 2020), glaucoma (Colasanti, 1990), psoriasis (Wilkinson & Williamson, 2007), and fungal infections (Eisohly et al., 1982).

The objectives of our study were twofold. First, we looked to evaluate the pharmacokinetics of CBGA and CBG using a 24-h pharmacokinetic analysis and a determination of steady-state levels after 2 weeks of treatment in each the fed and fasted states. Second, we aimed to evaluate the safety of these compounds in the dog over the two-week trial with physical examination (including heart rate), complete blood counts, and serum chemistry evaluations.

2 | METHODS

2.1 | Animals

Six intact male beagles all 2 years of age weighing between 18.6 and 22.2 kilograms body weight were housed at the Baker Institute for Animal Health, and all procedures were approved by the Cornell University Institutional Animal Care and Use Committee (Protocol 2019–0001).

2.2 | Protocol

All dogs underwent the fasted treatment trial for a two-week period. Dosing was performed using a 1 cc dosing syringe that was placed at the back of the tongue near the pharynx for treatments (between 0.28 and 0.34 ml delivered) to ensure complete ingestion of the dose delivered. After Day 14 of treatment, the dogs were allowed 2 weeks of washout. After this washout period, dogs began a 2-week period of similar treatment in the fed state where they were dosed and then provided ¼ of a 13 ounce can of a wet food (Purina Pro Plan Savory Chicken and Rice Formula, Nestle Purina, St. Louis, MO) immediately after dosing.

Twenty-four-hour pharmacokinetic analysis of serum cannabinoid levels was performed on Day 1 after a single dose in the fed or fasted state. Starting on day two, twice daily dosing of treatment oil at both 7 am and 7 pm was administered for and serum cannabinoids were measured at one week and two weeks for each phase of the study 6 h after morning dosing on Days 7 and 14. Two milliliters of blood was drawn via jugular venipuncture for all 6 dogs prior to the initial dose (0 h) and then again at 0.5, 1, 2, 4, 8, 12, and 24 h for the 24-h pharmacokinetic analysis.

One day before the study initiation, all dogs had blood drawn for a complete blood count and serum chemistry and again at the end of each phase of the 2-week study. Automated complete blood counts were performed using an Advia 2125 (Siemens, Munich, Germany) to assess white blood cells [WBC], hematocrit, hemoglobin, red blood cells [RBC], neutrophils, lymphocytes, platelets, monocytes, eosinophils, and basophils, and serum biochemistry analyses were performed using a Cobase 6000 (Roche, Basel, Switzerland; sodium, potassium, chloride, magnesium, calcium, phosphorus, albumin, total protein, globulin, urea nitrogen, creatinine, alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate amino transferase [AST], cholesterol, total bilirubin, glucose, and gamma glutamyl

transferase [GGT]). Both analytic tests were performed by the Cornell University Diagnostic Laboratory Clinical Pathology Service. The dose administered at each dosing interval was 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA from a *C. sativa*. cultivar devoid of CBD or THC synthase from a commercial facility (Cultivate Biologics, Holly, CO) using a blend of heated and unheated cold ethanol extracted whole flower in a sesame oil base, which was tested again at the end of the study showing virtually the same analytical profile.

2.3 | Physical examination

Prior to enrollment, all dogs involved in the study were deemed healthy based on physical examination; behavioral observations were performed on Day 1, Day 3, Day 7, and Day 14, 2 h after morning dosing for each phase of the trial. Physical examination included vitals measurements and a complete neurological examination including hopping response, menace, and pupillary light reflexes. Behavioral examinations were performed to assess for adverse events including lethargy, somnolence, ataxia, or abnormal behavior and dog interaction within the colony. Vomiting and diarrhea were also assessed and recorded in daily logs of the colony. Due to the potential for CBG/CBGA to affect heart rate, dogs were assessed manually for resting heart rates for 30 s using auscultation of the heart via stethoscope counts and extrapolated to relative beats per minute after initial dosing at time points 0, 1, 2, 4, 12, 24, and 48 h and again at Day 7 and Day 14 after morning dosing for both the fed and fasted arms of the study.

2.4 | Serum cannabinoids analysis

Analysis was performed using an exploratory (fit-for-purpose) method for fast measurement of thirteen cannabinoids and their metabolites at the Toxicology Research Laboratory, University of Illinois at Chicago. The reference standards for CBD and CBDA were obtained from Restek Corporation; all other reference and internal standards including CBG and CBGA were obtained from Cerilliant Corporation. Cannabinoids (CBD), CBDA, 7-COOH Cannabidiol (7-COOH-CBD), THC, THCA, cannabinol (CBN), cannabichromene (CBC), CBG, and CBGA and their metabolites (7-OH-CBD, 7-COOH-CBD, COOH-THC, and COOH-THC-Glu) concentration in dog serum was determined using high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Nexera X2 and LCMS 8050, Shimadzu Corp.).

Dog serum (40 µl) was mixed with 20 µl of internal standards [100 ng/ml of CBD-d3, THC-d3, THCA-d3, 7-COOH-CBD-d3, COOH-THC-d9, and COOH-THC-Glu-d3 in water:methanol (50:50)] in a 96-well plate. Proteins were precipitated, and compounds were extracted by adding 100 µl of ice-cold acetonitrile to the samples, then vortexing for 1–2 min, and centrifuging at 1900 *g* for 10 min at 4°C. Supernatants (70 µl) were mixed with 70 µl of water in a different 96-well plate and centrifuged again. Ten µl of the processed samples was injected into Waters Atlantis T3 HPLC column (3 µm 2.1 × 50 mm) with a guard cartridge (Waters VanGuard Atlantis T3) coupled to LC-MS/MS. The column was equilibrated with mobile phase A (0.1% formic acid in water) and mobile phase B (acetonitrile) at 50% B. The compounds were eluted by a linear gradient from 50% B to 95% B over 6 min and then held at 95% B for 1 min. Subsequently, the column was re-equilibrated at initial composition for 1 min at a flow rate of 0.3 ml/min. The autosampler and column temperature were set a 4°C and 30°C, respectively. The compounds were detected in electrospray ionization positive and/or negative mode. Interface voltage and temperature were 4 kV and 300°C, respectively. Desolvation line and heat block temperatures were 250°C and 400°C, respectively. Nebulizing, heating, and drying gas flow were 2.7, 5, and 5 L/min, respectively.

Concentrations of cannabinoids were calculated by LabSolutions software (Shimadzu Corp. using a quadratic calibration curve with $1/c^2$ weighing based on relative response (peak area of cannabinoids/peak area of internal standards). Measurable cannabinoids for pharmacokinetics in serum were CBG and CBGA. The range of the calibration curve for CBG was 0.5–1000 ng/ml with the lower limit of quantitation being 0.5. The CBGA calibration curve range was 1–1000 ng/ml with the lower limit of quantitation being 1 ng/ml.

2.5 | Pharmacokinetics and statistical analysis

The 24-h non-compartmental pharmacokinetic analysis of CBG and CBGA was performed utilizing a commercial software system. (PK solutions 2.0, Summit PK). Semi-log plots were utilized to determine linearity of the elimination profiles. The results generated were time to maximal concentrations (Tmax), maximum serum concentration (Cmax), elimination half-life (T ½), area under the curve to the last time-point ($AUC_{0\text{-}24}$), and mean residence time (MRT). The program predicts steady-state average, minimal and maximal and average concentrations with chronic administration based on the assumption that steady is achieved after five half-lives of administration (Css Ave).

Statistical analysis of the pharmacokinetic results was performed on fed versus fasted 24-h pharmacokinetic outcomes using a Wilcoxon-signed rank testing, as the CBG and CBGA data were not normally distributed as determined by Shapiro–Wilk testing. Similarly, complete blood count data and selected serum chemistry data (hepatic and kidney parameters) from the dogs in each phase were compared at baseline and 2 weeks for both the fed and fasted portions of study using a paired Student's *t*-test based on normal distribution of a majority of the parameters using Shapiro–Wilk analysis. A one-way analysis of variation was performed on the normally distributed heart rate assessments over time for each phase of the study (fed and fasted). A Friedman's analysis of variance was used to assess any significant differences in the CBG and CBGA in the fed and fasted states across Week 1 and Week 2 steady-state concentrations, due to lack of normality when Shapiro–Wilk testing was

performed. For all statistical testing, the p value was set at ≤0.05 as significant. All statistical testing was performed with GraphPad Prism 6.0 (Graphpad), and figures were generated using the same software. Any result that was below the quantifiable limit for the respective cannabinoid was considered 0 for all graphing and representation of data.

3 | RESULTS

3.1 | 24-h, 1- and 2-week pharmacokinetics

Twenty-four-hour PK analyses resulted in calculable Cmax (ng/ml), Tmax (h), elimination T1/2 life (h), AUC 0–24 (ng-h/ml), MRT (h), and predicted steady-state average means for CBG and CBGA. No other cannabinoid could be found at the detectable ranges. All data, means, and standard deviations for CBG as well as CBGA in the fed and fasted state are found in Tables 1 and 2, respectively. There were no statistically significant differences noted across all pharmacokinetic parameters when comparing the fed and fasted results (Table 1). The CBGA serum concentrations were far higher than found for CBG globally across all dogs and although not statistically significant, both CBG and CBGA concentrations are higher in the fasted state (Figure 1 and Figure 2). One- and two-week 6-h post morning dose of oil showed that CBG serum concentrations were 12.7 ± 12.3 SD ng/ml and 9.6 ± 8.4 SD ng/ml in the fed state, respectively, and 6.1 ± 6.0 SD ng/ml and 5.0 ± 3.5 SD ng/ml in the fasted state, respectively (p = .34; Figure 3). One- and two-week CBGA serum concentrations were 564 ± 574 SD ng/ml and 223 ± 197 SD ng/ml in the fed state, respectively, and 437 ± 414 SD ng/ml and 260 ± 300 SD ng/ml in the fasted state, respectively (Figure 4). All of these results are of a similar order to predicted steady-state concentrations observed from the pharmacokinetic analysis.

3.2 | Serum chemistry and complete blood counts

Mean and standard deviation serum chemistry and complete blood counts at baseline and Week 2 are shown in Tables 3 and 4, respectively, with no values for any parameters being outside of the normal reference range established by the Cornell Veterinary Diagnostic Laboratory Clinical Pathology Services. Serum chemistry changes associated with treatment with the cannabinoid and oil-based product suggest that there were very mild increases in the fed and fasted state for serum creatinine ($p < .01$ fasted; $p < .01$ fed). Serum albumin ($p = .03$), cholesterol ($p = .03$), and AST ($p = .01$) levels also show a significant increase during the fed phase at Week 2, while serum ALP (fasted $p = .02$; fed $p = .05$) shows a decrease during the fed and fasted phases at Week 2. No other significances were noted among remaining kidney and hepatic parameters. Serum electrolytes showed no significant differences across time with treatment (data not shown).

Complete blood count data differences were noted for white blood cell counts with higher counts at Week 2 during both the fed

TABLE 1 Mean and standard deviations ($n = 6$) on serum 24-h pharmacokinetic values of CBG fed and fasted states. p values at bottom represent comparisons between fed and fasted states

CBG Fed	Cmax (ng/ml)	Tmax (h)	T1/2 el (h)	AUC (0–24 ng-h/ml)	MRT (hr)	Css Ave (ng/ml)
Beagle 1	20.5	1	1.99	61.9	3.2	6.3
Beagle 2	42.6	0.5	2.44	117.2	3.4	8.4
Beagle 3	38.3	0.5	2.17	123.9	3.2	9.8
Beagle 4	52.9	0.5	1.36	66.3	1.7	5.8
Beagle 5	33.6	1	1.45	49.4	2.3	5.3
Beagle 6	46.5	1	1.38	81.5	2.4	9.3
Mean ± SD	39.1 ± 11.3	0.75 ± 0.27	1.80 ± 0.46	83.4 ± 30.6	2.7 ± 0.7	7.5 ± 1.9
CBG Fasted						
Beagle 1	85.4	0.5	2.9	166.4	4	14.7
Beagle 2	26	2	2.22	83.2	3.4	8.2
Beagle 3	55.4	0.5	2.22	106.1	3.1	9.6
Beagle 4	43.6	1	2.18	100.5	3.1	9.4
Beagle 5	43.9	1	1.39	63.7	1.8	5.4
Beagle 6	73	1	1.54	73	2.1	11.6
Mean ± SD	54.7 ± 21.5	1 ± 0.5	2.1 ± 0.5	98.8 ± 36.8	2.9 ± 0.8	9.8 ± 3.1
p value	0.31	0.75	0.06	0.22	0.13	0.69

Note: No significant differences found between fed and fasted states.

Abbreviations: AUC (0–24), Area under the serum concentration curve to 24 h; Cmax, maximum serum concentration; Css Ave, Predicted average steady-state serum concentration; MRT, Mean residence time; T1/2, Half-life of elimination; Tmax, Time to a maximal concentration.

TABLE 2 Mean and standard deviation concentrations ($n = 6$) on serum 24-pharmacokinetics values of CBGA fed and fasted states. p values at bottom represent comparisons between fed and fasted states

CBGA Fed	Cmax (ng/ml)	Tmax (h)	T1/2 el (h)	AUC (0–24 ng-h/ml)	MRT (hr)	Css Ave (ng/ml)
Beagle 1	737	1	1.99	2275	3.3	228
Beagle 2	1866	0.5	2.27	3722	2.8	361
Beagle 3	1816	0.5	1.01	5469	2.2	759
Beagle 4	2191	0.5	1.69	2890	1.9	243
Beagle 5	1336	1	1.59	1890	2.2	180
Beagle 6	1890	1	1.32	3224	2.3	353
Mean ±SD	1639 ± 521	0.75 ± 0.27	1.64 ± 0.45	3245 ± 1271	2.5 ± 0.5	353.8 ± 211.0
CBG Fasted						
Beagle 1	2998.6	0.5	3.43	5580	5.2	528
Beagle 2	1082.3	2	2.27	3648	3.5	351
Beagle 3	2482.9	0.5	2.11	4752	2.9	420
Beagle 4	1891.8	1	2.18	4589	3.1	429
Beagle 5	1638.9	1	1.75	2460	1.9	184
Beagle 6	3352.1	1	1.36	5588	1.9	520
Mean ± SD	2241.1 ± 859.5	1 ± 0.5	2.2 ± 0.7	4436 ± 1207	3.1 ± 1.2	405 ± 127
p Value	0.21	0.75	0.44	0.68	0.81	0.31

Note: No significant differences found between fed and fasted states.

Abbreviations: AUC (0–24), Area under the serum concentration curve to 24 h; Cmax, Maximum serum concentration; Css Ave, Predicted average steady-state serum concentration; MRT, Mean residence time; T1/2, Half-life of elimination; Tmax, Time to a maximal concentration.

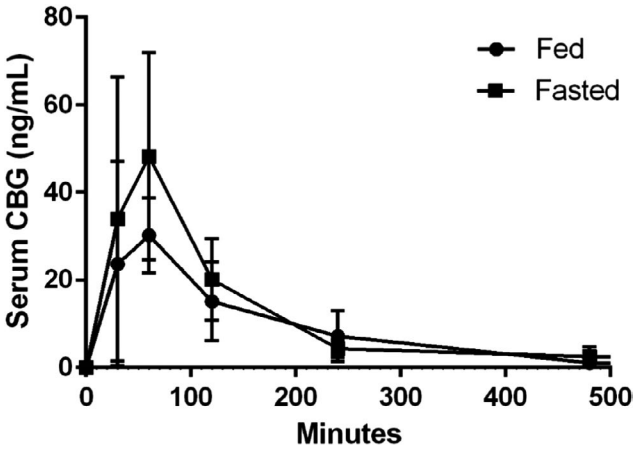

FIGURE 1 Serum concentrations of CBG (mean and standard deviation) after oral administration in dogs receiving 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA hemp extract comparing fed versus fasted. No significant difference between fasted and fed states was observed

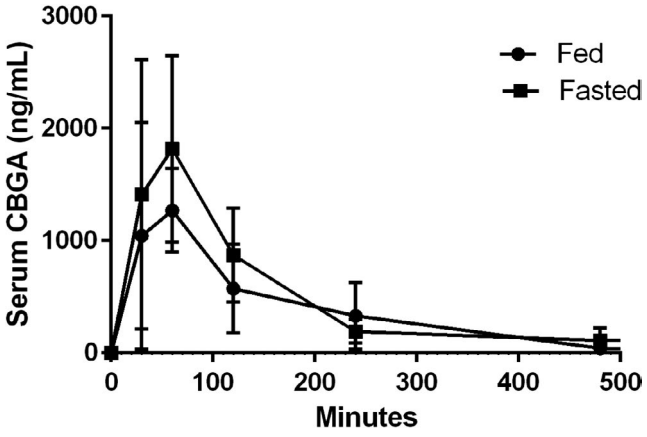

FIGURE 2 Serum concentrations of CBGA (mean and standard deviation) after oral administration in dogs receiving 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA hemp extract comparing fed versus fasted. No significant difference between fasted and fed states was observed

and fasted states (fasted $p = .02$; fed $p = .01$). Similarly, when examining specific cell types, neutrophils were found to be increased at Week 2 after each phase of treatment (fasted $p = .02$; fed $p = .01$). Platelets and monocytes were significantly increased at Week 2 during the fasted phase of the trial ($p < .01$). Hematocrit concentration was found to be significantly increased in the fed state 2 weeks after treatment ($p = .01$).

3.3 | Dog health and heart rate

Physical examinations performed throughout found no observable abnormalities regarding activity, neurological deficits, or behavior at any stage of the study. Vomiting was noted in 1 dog on day two after morning dosing of the fasting phase with no other changes in appetite, vomiting, or diarrhea observed throughout the treatment

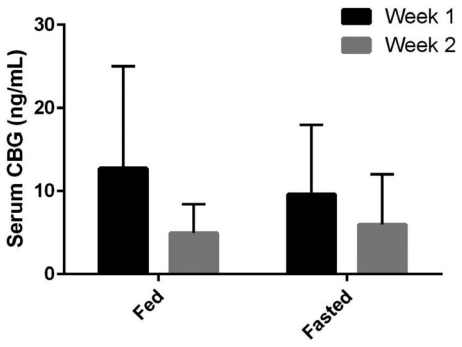

FIGURE 3 One- and two-week serum CBG concentrations (mean and standard deviation) 6 h after morning dosing with an oral product that is an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA hemp extract at a dose of 2 mg/kg body weight delivered BID, comparing fed versus fasted. No significant difference was found between weeks or fed/fasted states

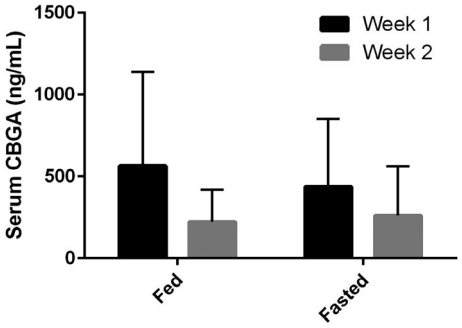

FIGURE 4 One- and two-week serum CBGA concentrations (mean and standard deviation) 6 h after morning dosing with an oral product that is an equal mix of 30 mg/ml CBG and 30 mg/ml C BGA hemp extract at a dose of 2 mg/kg body weight delivered BID, comparing fed versus fasted. No significant difference was found between weeks or fed/fasted states

phases of the study. The heart rate observed during the two-week period across both phases of the trial is found in Table 5. No significant differences were noted across the fed and fasted phases of the trial.

4 | DISCUSSION

This is the first pharmacokinetic serum assessment of CBG and CBGA using an infused sesame oil that contained a mixture of 30 mg/ml CBG and 30 mg/ml CBGA given orally to dogs. Recently, there has been an increased use of oral hemp products in pets that contain CBD and/or the acidic form CBDA in veterinary medicine through many vendors, but some also contain variable amounts of CBG or CBGA (Wakshlag, Cital, et al., 2020). Cultivars that specifically synthesize primarily CBG or its acid derivative are likely to be developed for nutraceutical sales. It is important to evaluate the CBG and CBGA in companion animals, such as the dog, to better understand the pharmacokinetics and utility of these products, particularly in light of NSAID intolerance and the need for safe alternatives for pain control.

TABLE 3 Serum chemistry mean and standard deviation concentrations ($n = 6$) at 0 and 2 weeks during the fed and fasted states for dogs receiving 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA hemp extract

Serum biochemistry (reference range)		Baseline	2 weeks	*p* value
Total Protein	Fed	5.9 ± 0.2	6.1 ± 0.3	.17
(5.5–7.2 g/dl)	Fasted	5.8 ± 0.2	6.1 ± 0.3*	.04
Albumin	Fed	3.7 ± 0.2	3.9 ± 0.1*	.03
(3.2–4.1 g/dl)	Fasted	3.6 ± 0.2	3.8 ± 0.2	.06
Globulin	Fed	2.3 ± 0.2	2.3 ± 0.2	.79
(1.9–3.7 g/dl)	Fasted	2.2 ± 0.2	2.3 ± 0.2	.14
Creatinine	Fed	0.7 ± 0.1	0.8 ± 0.1	<.01
(0.6–1.4 mg/dl)	Fasted	0.7 ± 0.1	0.8 ± 0.1	<.01
Urea Nitrogen	Fed	15 ± 3	17 ± 3	.21
(9–26 mg/dl)	Fasted	14 ± 3	15 ± 3	.36
ALT	Fed	27 ± 4	29 ± 6	.11
(17–95 U/L)	Fasted	26 ± 5	30 ± 6	.06
AST	Fed	27 ± 6	32 ± 4*	.01
(18–56 U/L)	Fasted	27 ± 3	32 ± 6	.08
ALP	Fed	43 ± 17	38 ± 13*	.05
(7–115 U/L)	Fasted	47 ± 16	41 ± 15*	.02
Cholesterol	Fed	209 ± 42	239 ± 38*	.03
(136–392 mg/dl)	Fasted	199 ± 47	191 ± 36	.32
Glucose	Fed	91 ± 8	106 ± 14	.06
(68–104 mg/dl)	Fasted	95 ± 7	89 ± 8	.10
Total Bilirubin	Fed	0.1 ± 0.1	0.1 ± 0.0	.17
(0.0–0.2 mg/dl)	Fasted	0.1 ± 0.0	0.1 ± 0.1	.17
GGT	Fed	2 ± 1	1 ± 1	.32
(0–8 U/L)	Fasted	2 ± 1	1 ± 1	.45

Note: References ranges based on Cornell Veterinary Diagnostic Laboratory and asterisk denotes a significant difference.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase, ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

Human literature reports a variety of potential beneficial effects with CBG as it works upon many receptors (Deiana, 2017). In addition to its potential effects on the endocannabinoid system, it also acts on the adrenergic, serotonergic, and transient receptor potential receptors (Deiana, 2017). Anti-inflammatory and anti-cancer effects have been noted in the literature as potential therapeutic effects (Borrelli et al., 2013, 2014). More recently, CBGA has been evaluated for its antiepileptic activities in children (Anderson, Heblinski, et al., 2021). However, CBGA research is sparse as most research has been on CBG or vaporized/smoked hemp, which contains only decarboxylated forms of this cannabinoid.

Our 24-h pharmacokinetic examination of CBG and CBGA demonstrates a marked increase in CBGA concentrations when

compared to CBG in dog serum. CBGA levels in the serum show approximately 40 times higher Cmax when compared to CBG in both the fed and fasted states, with similar Tmax and T ½ lives for both compounds. In the limited human literature, there is little focus on the acidic forms and oral consumption makes this study novel in a higher mammalian species examining the pharmacokinetics of CBG and CBGA showing definitive superiority in absorption and retention of CBGA. This follows the path of previous work which demonstrated that CBDA and THCA reached higher serum concentrations than that of CBD or THC in dogs (Wakshlag, Schwark, et al., 2020). Literature in human medicine has not examined the absorption and elimination of the acidic forms of the common cannabinoids such as THCA and CBDA which is in its infancy as commonly delivered cannabinoids with recent work, suggesting that CBDA is absorbed particularly well in a whole hemp extract (Anderson, Etchart, et al., 2021; Deabold et al., 2019; Łebkowska-Wieruszewska et al., 2019; Wang et al., 2016). Precisely how and why the acidic forms of the cannabinoids are absorbed better has yet to be elucidated, but it has been postulated that CBDA is absorbed better as a whole hemp extract due to other cannabinoids preventing efflux from the intestinal epithelium allowing for higher Cmax values when compared to providing CBDA isolate (Anderson, Etchart, et al., 2021). As our extract did have CBG as a component that is thought to prevent efflux from intestinal epithelium, it may actually be that the CBG itself is promoting better absorption of CBGA which needs further elucidation.

Prevailing thought until recently was that the volatility of carboxylated forms of cannabinoids would be sensitive to storage and gastric pH resulting in metabolism to the decarboxylated cannabinoids (Eichler et al., 2012; Hložek et al., 2017). This can largely be ignored based on our results and recent results in dogs and humans showing absorption in the native form have typical pharmacokinetics similar to CBD and CBG, albeit reaching far higher concentrations (Anderson, Etchart, et al., 2021; Wakshlag, Schwark, et al., 2020). The time to Tmax for CBG and CBGA is identical regardless of being fed or fasted, suggesting that these cannabinoids follow similar absorption kinetics of other species and absorption of CBD and CBDA in the dog (Wakshlag, Schwark, et al., 2020).

When comparing the fasted versus fed state, no statistical difference was observed. However, when visually evaluating the data, the fasted state did show higher mean serum levels of both CBG and CBGA, with large standard deviations. These findings differ from previous work completed on other cannabinoids (CBD and THC) where the fed state resulted in higher absorption rates (Wakshlag, Schwark, et al., 2020); however, direct comparisons to fed and fasted absorption of CBD have not been published in the dog. In fact, CBD and THC both show definitive increases when administered during feeding in primates, rats, and humans, particularly when administered in a fatty meal (Birnbaum et al., 2019; Perlin et al., 1985). Though speculative, the differences may lie in the polarity of the molecules whereby CBD and CBDA may be more hydrophobic than CBG or CBGA resulting in superior absorption of CBGA in particular. This is evidenced by the very high serum concentrations observed in the short and two-week dosing of CBGA which when compared to prior CBDA published concentrations, are nearly fourfold to fivefold higher after a similar single dose. After 2 weeks of twice daily dosing, the serum concentrations of CBGA are over twofold higher when compared to CBDA concentrations suggesting fundamental differences between these molecules regarding absorption in the dog (Wakshlag, Schwark, et al., 2020).

The pharmacokinetics of CBG and CBGA over a 2-week period shows absorption and retention after oral dosing in both the fasted and fed states. However, the CBGA is absorbed at a much higher concentration and maintains a far higher serum concentration when

TABLE 4 Complete blood count means and standard deviations ($n = 6$) at 0 and 2 weeks during the Fed and Fasted states for dogs receiving 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CBGA hemp extract

Complete blood count (Reference range)		Baseline	2 weeks	*p* value
WBC	Fed	6.1 ± 0.7	7.1 ± 1.0*	.01
(5.7–14.2 thou/uL)	Fasted	6.0 ± 1.0	6.8 ± 1.0*	.02
HCT	Fed	54 ± 2	57 ± 3*	.01
(41%–58%)	Fasted	59 ± 2	58 ± 2	.36
Hemoglobin	Fed	19.5 ± 0.5	19.3 ± 0.7	.69
(14.1–20.1 g/dl)	Fasted	18.5 ± 0.7	19.1 ± 0.3	.26
RBC	Fed	8.2 ± 0.3	8.2 ± 0.2	.63
(5.7–8.5 mill/μl)	Fasted	7.6 ± 0.4	8.1 ± 0.3	.06
Platelets	Fed	270 ± 27	296 ± 68	.19
(186–545 thou/μl)	Fasted	232 ± 13	280 ± 24*	<.01
Neutrophils	Fed	3.5 ± 0.8	4.5 ± 1.1*	.01
(3.0–9.6 thou/μl)	Fasted	3.6 ± 0.7	4.2 ± 1.0*	.02
Lymphocytes	Fed	2.1 ± 0.6	2.1 ± 0.6	.42
(1.1–4.5 thou/μl)	Fasted	2.0 ± 0.1	2.0 ± 0.5	.91
Monocytes	Fed	0.2 ± 0.1	0.3 ± 0.1	.61
(0.1–1.0 thou/μl)	Fasted	0.2 ± 0.1	0.3 ± 0.1*	<.01
Eosinophils	Fed	0.3 ± 0.1	0.2 ± 0.1	.46
(0.1–2.1 thou/μl)	Fasted	0.2 ± 0.0	0.2 ± 0.0	.11

Note: References ranges based on Cornell Veterinary Diagnostic Laboratory and asterisk denotes a significant difference.

TABLE 5 Mean and standard deviation ($n = 6$) for auscultated manually counted heart rate at 9 points in time during the fed and fasted states for dogs receiving 2 mg/kg body weight of an equal mix of 30 mg/ml CBG and 30 mg/ml CGBA hemp extract

Manual HR	0 h	1 h	2 h	4 h	12 h	24 h	48 h	1 week	2 week	*p* value
Fed	107 ± 9	108 ± 8	113 ± 4	111 ± 6	105 ± 8	108 ± 5	107 ± 7	108 ± 9	109 ± 7	.77
Fasted	107 ± 7	105 ± 11	104 ± 11	105 ± 8	102 ± 11	104 ± 7	103 ± 11	103 ± 8	103 ± 9	.14

compared to CBG. Comparatively, this makes CBGA a better pharmacologic molecule since its absorption and retention appear to be nearly 10-fold higher than what can be achieved with CBG. Although there were no significant differences between the weeks or fed/fasted states of CBG nor CBGA in our small study, the *p* value over time for CBGA was 0.11 which points toward potential differences over time, which may or may not be clinically relevant. Interestingly, week two concentrations are lower than week one regardless of the fed or fasted state, suggesting that there may be alterations in hepatic metabolism that occur at the initiation of dosing which may lead to the disposal of CBG in urine or bile that warrant further investigation of cytochrome p450 enzymatic induction or inhibition.

CBG and CBGA given orally at 2 mg/kg twice daily for 2 weeks appear to be very safe for dogs. Physical examination did not reveal any changes in behavior, neurologic status, or activity levels. No psychotropic effects would be anticipated with CBG or CBGA administration as would be expected with THC, as CBG and CBGA have never been found to activate the cannabinoid 1 and 2 receptor systems, rather they act as an antagonist (Cascio et al., 2010). Serum biochemistry evaluation of the fed state at the 2-week period revealed mild significant elevations in albumin, creatinine, AST, and cholesterol. Creatinine also had mild, yet significant elevation in the fasted state. However, none of these variations were outside of the reference range. More importantly, rises in liver enzymes were absent in our population. ALP, in particular, was observed to decrease in both the fasted and fed states. This is in contrast to previous veterinary studies in which ALP levels became elevated after ingesting CBD. In one study, where the dogs were given 10 and 20 mg/kg for a period of 6 weeks, significant elevations in ALP occurred (McGrath et al., 2018). A clinical trial evaluating CBD oil at 2 mg/kg twice daily for osteoarthritis pain management led to 9 dogs having elevations in ALP that were outside of the reference range (Gamble et al., 2018), while similar observations were seen in a 3-month refractory seizure study (McGrath et al., 2019). However, the dogs in this study were primarily geriatric and on other concurrent medication compared to our population of healthy dogs. Presumably, CBD causes this elevation due to upregulation of the cytochrome p450 enzyme oxidative hepatic metabolism with chronic administration which may lead to increased elimination in urine or bile (Bornheim & Correia, 1989). CBG and CBGA may not cause the same level of upregulation of cytochrome p450 and may not be as potent at inducing the cytochrome p450 system as CBD, which warrants further investigation into metabolism and elimination of CBG and CBGA.

When evaluating the complete blood counts, there were mild but significant increases in white blood cell count and neutrophils in both fasted and fed states at the 2-week point compared to the baseline. Platelets and monocytes were significantly increased in the fasted state only. The hematocrit was elevated in the fed state only. While statistically significant alterations occurred, none were clinically relevant as they did not fall outside of the reference ranges. It is unknown if the elevation in white blood cell count and neutrophils is secondary to immune stimulus of CBG or CBGA or if it could be secondary to the oil used as the vehicle for administration. These findings are tenuous since a major limitation of our study was that there was no placebo treatment during this trial therefore the effects on serum chemistry alterations and complete blood counts could be due to the small amount of sesame oil as the base of the hemp supplement provided. Additionally, the dogs used in this study were a small, homogeneous population which may not reflect companion dogs with comorbidities. However, the pharmacokinetic results do suggest that CBG and/or CBGA appear to be absorbed and retained at potentially pharmacologically relevant levels when compared to receptor kinetics data (Turner, 2017).

Physiologically, CBG is known to act as an agonist upon α-2 adrenergic receptors (Nachnani et al., 2021). Other α-2 adrenergic agonists such as dexmedetomidine can induce cardiovascular effects such as alterations in blood pressure and reflex bradycardia (Granholm et al., 2007). The dogs were followed for bradycardia throughout the initial dosing and over the two-week period of treatment finding no significant changes in heart rate. It may be that the low dose and poor absorption of CBG globally resulted in a lack of α-2 adrenergic stimulation and we can safely assume that the CBGA molecule does not induce significant bradycardia upon oral absorption in our small cohort; however, the manual handling of the dogs does lead to excitement that may have masked any subtle effects.

It has been found that the complex, bioactive molecules that make up the hundreds of cannabinoids have synergistic effects, also known as the "entourage effect." It is suggested that interactions between these hemp constituents can alter plasma concentrations as a recent study showed a 14-fold increase in CBDA concentration following administration of a cannabis extract when compared to the same molecule being administered alone (Anderson, Etchart, et al., 2021). Our study consisted of a hemp extract consisting only of CBG and CBGA without measurable THC, CBD, THCA, CBDA, or CBC based on our third party analysis; therefore, results may vary if other CBG rich whole hemp extract containing only CBG or CBGA were used. Our results are merely the results of one specific product that cannot be extrapolated to other products or extracts of CBG and CBGA with our results, suggesting that further research into acidic form may be fruitful based on the pharmacokinetics observed in this study.

In conclusion, this study is the first to show that CBG and CBGA hemp extract given orally at 2 mg/kg twice daily administration in sesame oil for 2 weeks is absorbed and retained in the dog. Further studies are necessary to understand elimination kinetics and long-term treatment concerns; however, CBGA is much more absorbable and retains a higher serum concentration for a greater length of time, making it more likely to have pharmacologic benefits. Both CBG and CBGA appear to be safe upon short-term evaluation of serum biochemistry, blood count, physical examination, and heart rate monitoring in a healthy population of dogs. This specific hemp extract appears to be safe for short-term consumption and caution should be taken when making direct comparisons with other products due to differences in hemp constituents, carrier oils utilized or other emulsions. Clinical trials to evaluate the pharmacologic benefits of CBG and CBGA in painful, neurologic, and inflammatory conditions

are warranted, and a focus on the acidic form may be worthwhile due to the absorption kinetics observed.

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CONFLICTS OF INTEREST

JJW is a paid consultant for Ellevet Sciences, and WSS is an advisory board member for Ellevet Sciences. All other authors have no conflicts of interest.

AUTHOR CONTRIBUTION

JJW was involved in all aspects of the project and publication. KPV, KE, KA were all involved in treatment, data collection, data analysis and manuscript preparation. WSS was involved in data analysis and manuscript preparation and revision. AL, BG, AZ were involved in sample analysis, data collection, data analysis and manuscript preparation and revisions.

ANIMAL ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The authors confirm that they have adhered to US or standards for the protection of animals used for scientific purposes.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

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