

# Effects of Administration of Carnivora™ on Clinical Signs in Cats After Repeat Challenge with Feline Herpesvirus 1

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## ABSTRACT

Feline herpesvirus 1 (FHV-1) infection is a common and highly contagious feline upper respiratory pathogen, and vaccinated or previously infected cats can become ill upon re-exposure. Carnivora™ is a nutraceutical product with anti-inflammatory and immune system modulating properties. The objective of this study was to determine whether cats receiving Carnivora™ prior to FHV-1 repeat challenge, would have lessened clinical signs and viral shedding when compared to those cats receiving a placebo. Young adult cats previously inoculated with FHV-1 were randomized into either a treatment or placebo group approximately 1 year after the previous FHV-1 infection. Treatment or placebo was administered as recommended by the manufacturer for 56 days prior to FHV-1 challenge.

Cats that were administered Carnivora™

had significantly less clinical manifestations of disease when compared to the control group. The results of this pilot study suggest that Carnivora™ is an immune modulator in cats and could play a role in lessening signs of FHV-1 infected cats when re-exposed to the virus. These effects could also be beneficial for the management of other infectious diseases in cats and warrant further study.

## INTRODUCTION

Feline herpesvirus 1 (FHV-1) infection is a common and highly contagious feline upper respiratory pathogen. FHV-1 infection can be subclinical or can result in severe clinical disease including fever, sneezing, nasal discharge, conjunctivitis, keratitis, cough, dyspnea, and occasionally death.<sup>1-5</sup> While FHV-1 infected cats can be clinically normal for periods of time, the infection can be reactivated by crowding, other concurrent diseases, and other forms of stress.<sup>4,6-9</sup> Immunity against FHV-1 is not complete; therefore, vaccinated or previously infected

**Table 1.** *Carnivora*<sup>TM</sup> dosing protocol

Cats < 4 kg	Cats ≥ 4 kg
Week 1 (Monday through Saturday)	Weeks 1 and 2 (Monday through Saturday)
Morning. 1 capsule with food or water	Morning. 2 capsules with food or water
Afternoon. 5 drops by syringe directly into mouth	Afternoon. 5 drops by syringe directly into mouth
Evening. 1 capsule with food or water	Evening. 2 capsules with food or water
Week 1 (Sunday)	Weeks 1 and 2 (Sunday)
Morning. 1 capsule without food	Morning. 1 capsule without food
Evening. 1 capsule without food	Evening. 1 capsule without food
Weeks 2, 3, 5, 7, 9, 10, 11 (Monday through Saturday)*	Weeks 3, 5, 6, 7, 9, 10, 11 (Monday through Saturday)*
Morning. 2 capsules with food or water	Morning. 2 capsules with food or water
Afternoon. 8 drops by syringe directly into mouth	Afternoon. 10 drops by syringe directly into mouth
Evening. 2 capsules with food or water	Evening. 2 capsules with food or water
Weeks 2, 3, 5, 6, 7, 9, 10, 11 (Sunday)	Weeks 3, 5, 6, 7, 9, 10, 11 (Sunday)
Morning. 1 capsule without food	Morning. 1 capsule without food
Evening. 1 capsule without food	Evening. 1 capsule without food
Weeks 4, 8, 12 (Monday through Saturday)	Weeks 4, 8, 12 (Monday through Saturday)
Morning. 1 capsule with food or water	Morning. 1 capsule with food or water
Evening. 1 capsule with food or water	Afternoon. 2 capsules
Weeks 4, 8, 12 (Sunday)	Evening. 1 capsule without food or water
No treatment	Weeks 4, 8, 12 (Sunday)
	No treatment

cats can become ill when re-exposed to FHV-1.<sup>10-12</sup> In addition, during periods of activation, FHV-1 can be shed again in ocular or respiratory secretions, potentially resulting in the infection of other cats.<sup>9</sup>

Currently, oral administration of famciclovir or topical administration of cidofovir (ocular cases) are considered by many veterinarians to be the optimal treatments for cats with clinical signs of FHV-1 associated disease.<sup>13-17</sup> A number of strategies with variable outcomes have been employed in an attempt to lessen FHV-1 reactivation in cats.<sup>18</sup> Lessening stress, administration of lysine, and feeding an immune enhancing probiotic have been recently studied or reviewed.<sup>7,19,20</sup> Feeding of the immune-enhancing probiotic, administration of alpha 2b interferon, and use of an intranasal vaccine as a potential immune therapy, have provided information suggesting that immune modulation could be effective for the treatment or control of FHV-1.<sup>20,21</sup>

*Carnivora*<sup>TM</sup> is a commercial preparation derived from the extracts of *Dionaea muscipula*, the Venus fly trap carnivorous plant species.<sup>a</sup> The product contains compounds including naphthoquinones such as hydroplumbagin, plumbagin, and droserone, phenolic acids such as gallic acid, and flavonoids such as quercetin.<sup>22-25</sup> Studies have shown that *Carnivora*<sup>TM</sup> and these compounds have immune modulatory, anti-inflammatory, anti-cancer, and antiviral activities in vitro and some in vivo models.<sup>22,26-28</sup> *Carnivora*<sup>TM</sup> has also been used in some pets and has antiviral activity against herpes simplex type 2 of humans.<sup>24,26</sup> The hypotheses of this study were that treatment of cats with *Carnivora*<sup>TM</sup> would be safe and would lessen clinical signs of FHV-1 as well as viral shedding in cats who underwent repeat exposure inoculation to FHV-1.

## MATERIALS AND METHODS

### Treatment Groups

A total of 16 two-year-old cats were used

**Table 2. Clinical Scoring Chart**

Conjunctivitis	0 = None
	1 = Mild conjunctival hyperemia
	2 = Moderate to severe conjunctival hyperemia
	3 = Moderate to severe conjunctival hyperemia and chemosis
	0 = None
	1 = Eye < 25% closed
	2 = Eye 25 – 50% closed
	3 = Eye 50 to 75% closed
	4 = Eye completely closed
Ocular discharge	0 = None
	1 = Minor serous discharge
	2 = Moderate mucoid discharge
	3 = Marked mucopurulent discharge
Sneezing	0 = None
	1 = Observed
Nasal discharge	0 = None
	1 = Minor serous discharge
	2 = Moderate mucoid discharge
	3 = Marked mucopurulent discharge
Nasal congestion	0 = None
	1 = Minor congestion (barely audible)
	2 = Moderate congestion (easily audible)
	3 = Marked congestion with open mouth breathing
Body temperature (microchip)	0 = < 103 °F
	1 = > 103 °F

with Institutional Animal Care and Use Committee (IACUC) approval. One year before the study described here, each of the eight intact female and eight neutered male cats had been in a FHV-1, calicivirus, and panleukopenia vaccine study and were first infected with FHV-1 via aerosolization.<sup>29</sup> In that study, FHV-1 infection was confirmed in all cats and each developed clinical signs consisting of sneezing, ocular and/or nasal discharge, and/or conjunctivitis.

For use in this study, cats were randomized into a treatment group (n = 8) or control group (n = 8), and were individually kennelled in two separate rooms. The cats were provided dry food and water ad libitum and received daily group socializa-

tion. The treatment group was administered Carnivora™ orally as either capsules (1-2 capsules in morning, afternoon, and/or evening) or drops (5, 8, or 10 drops in morning, afternoon, and/or evening) following the manufacturers' instructions (Table 1). Body weights were measured weekly and doses for individual cats adjusted based on whether the body weight was above or below 4 kg. The control group of cats was administered saline and empty capsules in a similar volume, concentration, and manner to simulate the same degree of stress induced by medicating the treatment group of cats.

#### **Experimental Design**

Two trained, masked observers assessed

the cats for 30 minutes at approximately the same time in the mornings and recorded observations using a standardized score sheet consisting of seven variables, including body temperature (Table 2). Body temperatures were evaluated by subcutaneous microchip probe in 15 cats and axillary temperature in one cat due to two malfunctioning microchips.<sup>30</sup> Clinical scores were determined from Days -14 to 0 and Days 42 to 84, and temperatures were recorded from Days -11 to 0 and Days 42 to 84. For Days 0 to 42, the cats were observed daily for attitude and the presence of sneezing and ocular or nasal discharges, but a clinical score was not determined. Total number of clinical scores > 0 in the seven clinical score categories (Table 2), were compared between treatment and control groups, within each of the three treatment periods:

- pre-treatment equilibration period (14 days),
- pre-inoculation treatment period (15 days), and
- post-inoculation treatment period (28 days).

Body weights were measured weekly for all cats as a surrogate marker of appetite. To assess primary, stress-associated, or FHV-1 associated weight loss, the percent of increase or decrease in each cat's body weight between Day 0 and Day 84, between Day 0 and Day 56, and between Day 56 and Day 84, respectively, was assessed. The percent change in the different periods was compared between the treatment and placebo groups.

Blood was collected on Day -14 and Day 84 (Figure 1). Mucosal cells were collected from the caudal pharynx of each cat on Day 0, Day 56, Day 69, and Day 84 by gently rolling a swab against the mucosa in the region (oropharyngeal swabs) for performance of FHV-1 PCR assays. In addition, oropharyngeal swabs were also collected from individual cats on the first day after challenge that clinical signs were noted and then again 7 and 14 days later.

On Day 56, all cats were inoculated

with a USDA challenge strain of FHV-1 via nostril and oropharynx, as previously described.<sup>29</sup>

### **Clinical and Laboratory Evaluations**

On the day the samples were collected, total DNA and RNA was extracted, as previously described, from blood in EDTA. Samples were assayed for FHV-1 DNA using a previously described conventional FHV-1 PCR assay (cPCR).<sup>31</sup> Sera and oropharyngeal swabs were stored at -80°C until assayed in batches. Serum biochemical values were measured at a commercial laboratory.<sup>b</sup> Total DNA and RNA was extracted from the oropharyngeal swabs, and the FHV-1 cPCR assay was performed as well as quantitative PCR (qPCR) assays for FHV-1 DNA and GAPDH.<sup>16</sup>

Results of the FHV-1 qPCR assay were presented as the ratio of FHV-1 DNA/GAPDH DNA. Serum antibodies against FHV-1 were measured using a previously reported ELISA; the results were reported as absorbance values.<sup>32</sup> The pre and post-inoculation absorbance values were converted to a percent change value by use of the following formula: FHV-1 absorbance value post FHV-1 challenge/FHV-1 absorbance value pre FHV-1 challenge X 100.

### **Statistical Evaluation**

Fisher's exact test was used to compare total number of clinical scores > 0 (Table 2), between treatment and control groups, within each of the three treatment periods: pre-treatment equilibration period (14 days), pre-inoculation treatment period (15 days), and post-inoculation treatment period (28 days). The Shapiro-Wilk test was used to evaluate body weights, blood chemistry values, and FHV-1 titer changes for normality.

Due to non-normalcy, the Wilcoxon rank-sum test was used to compare body weight changes between the treatment and control groups; FHV-1 absorbance value changes between the treatment and control groups at start and end of study; and the treatment group's blood chemistry values at the start and end of study. Results of the FHV-1 PCR assays performed on DNA

extracted from blood and the oropharyngeal swabs were reported descriptively. Commercially available software was used for all comparisons.<sup>c</sup> Significance was defined as  $p < 0.05$ .

## **RESULTS:**

### **Serum Biochemistry**

There were no clinically significant differences when comparing serum biochemical values from the Carnivora<sup>TM</sup> treated cats before and after treatment.

### **FHV-1 associated clinical parameters**

#### *Equilibration period*

There were a maximum of 760 scores potentially collected during the 14-day equilibration period. One cat in the treatment group had a clinical score of 1 due to mild serous ocular discharge for 5 days, and one cat in the control group had a clinical score of 1 due to a sneeze on 1 day. All other cats had clinical scores of 0 every day. No cats in either room had temperatures above 103.0°F. The differences in cumulative total clinical scores between the treatment group (5 of 760 observations) and the control group (1 of 759 observations) were not statistically significantly different ( $p = 0.2$ ).

#### *Treatment period prior to FHV-1 challenge*

There were a maximum of 840 scores potentially collected during the 15-day treatment period prior to FHV-1 inoculation. The total clinical scores for the treatment group (3 of 840 observations) compared to the control group (13 of 840 observations) were significantly different ( $p = 0.02$ ). In the treatment group, there were a total of three occurrences of a clinical score of 1, due to sneezing from at least one cat. The other two sneeze occurrences were heard, but the specific cat was not identified.

In the control group, there were a total of 13 occurrences of a clinical score of 1. This included 12 occurrences in which the body temperature was above 103.0°F for three different cats and one episode of sneezing by one of these cats. The percentages of treatment cats with fever (0 of 8 cats; 0%) or any clinical sign (1 of 8 cats; 12.5%), were lower

than the percentages of control cats with fever (3 of 8 cats; 37.5%) or any clinical sign (3 of 8 cats; 37.5%), but these results were not statistically significantly different.

#### *Observation Period after FHV-1 Challenge*

There were a maximum of 1,568 scores potentially collected during the 28-day period after FHV-1 inoculation. The total clinical scores for the treatment group (5 of 1,568 observations) compared to the control group (37 of 1,568 observations) were significantly different ( $p < 0.0001$ ). In the treatment group, there were a total of five occurrences of a clinical score of 1. This included three sneezes from two cats and mild serous ocular discharge on 2 days from the same cat who had ocular discharge during the equilibration period.

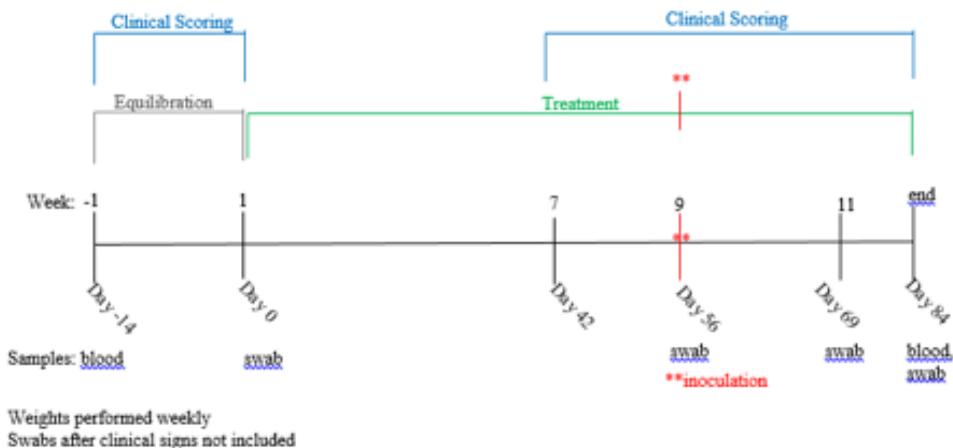
In the control group, there were a total of 37 occurrences of a clinical score of 1; this included 28 occurrences in which the body temperature was above 103.0°F for four different cats, and nine sneeze occurrences from those four cats and one other cat.

Overall, two of the treatment group cats (25%) accounted for all of the  $> 0$  scores after FHV-1 inoculation; one of these cats also accounted for all  $> 0$  scores during the equilibration period. Overall, five of the control group cats (63%) accounted for all of the  $> 0$  scores after FHV-1 inoculation; four of these cats had no  $> 0$  scores during the equilibration period. The percentages of treatment cats with fever (0 of 8 cats; 0%) or any clinical sign (3 of 8 cats; 37.5%) were lower than the percentages of control cats with fever (4 of 8 cats; 50%) or any clinical sign (5 of 8 cats; 62.5%), but these results were not significantly different.

#### *Body Weights*

Body weights on Day 0 were not significantly different ( $p=0.09$ ) when comparing the treatment group (median 4.6 kg; range 2.9-6.8) and the control group (median 3.3 kg; range, 2.4-5.5). All (94%;  $n=15/16$ ), but one of the cats experienced weight loss between Day 0 and Day 56. The amount of weight loss between Day 0 and Day 56 did not significantly differ ( $p=0.8$ ) when compar-

Figure 1. Treatment, monitoring and sampling schedule



ing the treatment group (median -8%; range -20% to 1%) and the control group (median -10%; range -22% to -3%). Weight changes potentially related to FHV-1 infection between Day 56 and Day 84, also did not significantly differ ( $p=0.4$ ) when comparing the treatment group (median -6%; range -14% to 3%) and the control group (median 0%; range -21% to 18%). Overall weight changes between Day 0 and Day 84 also did not significantly differ ( $p=0.4$ ) when comparing the treatment group (median -12%; range -31% to -4%) and the control group (median -8%; range -30% to 7%).

#### FHV-1 PCR Assays.

None of the cats were positive for FHV-1 DNA in blood by cPCR assay. From oropharyngeal swabs, one control cat was positive for FHV-1 via cPCR, both during the equilibration period and after FHV-1 re-inoculation; the cat was also positive for FHV-1 DNA via qPCR assay during the equilibration period. Prior to inoculation, after 8 weeks of treatment, one cat from the control group and one cat from the treatment group were positive for FHV-1 via qPCR assay. After FHV-1 inoculation, three cats from the control group (37.5%) were positive for FHV-1 via qPCR assay, but none of the treatment group (0%) were positive for FHV-1 via qPCR assay. The difference

was not significantly different. There were not enough positive samples to statistically compare magnitude of FHV-1 DNA shedding between groups.

Four cats in the treatment group and three cats in the control group had increased FHV-1 antibody absorbance values in the final sample when compared to the pre-treatment sample. However, the percentage changes between the groups were not statistically different ( $p = 0.9$ ).

## DISCUSSION

Cats that received Carnivora™ had fewer clinical signs of feline herpesvirus 1 when compared to those cats that received the control. Carnivora™ was also well tolerated, as neither vomiting nor diarrhea was reported by the research facility. In addition, there were no significant differences in serum biochemical panel findings in the Carnivora™ treated cats over the study. These results confirm unpublished observations that Carnivora™ is safe to use in cats at the doses and intervals described.

Several of the compounds found in extracts of *Dionaea muscipula*, including the naphthoquinones such as hydroplumbagin, plumbagin, and droserone, the phenolic acids such as gallic acid, and the flavonoids such as quercetin could have positive effects on viral infections in cats.<sup>25-28,33</sup>

In particular, plumbagin and quercetin have been shown to inhibit inflammatory cytokines and to have immunomodulatory, antimicrobial, and antiviral activity. Those potential positive effects associated with Carnivora™ were demonstrated in the cats described here when it was shown that the cumulative clinical scores were lower in Carnivora™ treated cats when compared to controls after repeat exposure to FHV-1.

In contrast, the clinical scores did not vary between the groups during the equilibration period. Overall, the percentage of cats developing clinical signs of activated FHV-1 after challenge was numerically greater in the control group (62.5%) than in the treatment group (25%). The failure to achieve statistical significance may reflect that small sample size.

In this study, the clinical signs after FHV-1 challenge were mild, as expected, as the cats were previously infected and should have had partial immunity. The results of the study document that FHV-1 immunity is not complete nor sterilizing as many cats became ill and shed FHV-1 again. Fever was common in the control cats but never detected in the treatment cats. While FHV-1 viremia was not detected in these cats, the PCR assay on blood was not performed on the days that fevers were present. Thus, we cannot confirm a correlation between fever and viremia. It is possible that local inflammation in the upper respiratory tract was adequate to induce a febrile response.

After FHV-1 challenge, three of the control cats but none of the treatment cats had repeat FHV-1 shedding. These results suggest a treatment response induced by Carnivora™. However, the results will need to be confirmed in a larger study, as this result was not statistically significant using this sample size. In this study, FHV-1 antibody absorbance values increased in four treatment cats and three control cats, and there was no difference in the magnitude of the antibody changes between groups. Thus, it could not be documented whether Carnivora™ administration potentiated FHV-1

humoral immunity.

In a different study of an immune-enhancing probiotic, FHV-1 antibody titers were not enhanced. It was proposed in that study that the cats were healthy and immune competent and thus, already had titers close to maximal, potentially masking a treatment effect.<sup>20</sup> That hypothesis may also be true for this study.

Plumbagin, one of the metabolites in Carnivora™, has been shown to prevent weight loss in mice models.<sup>34</sup> Thus, we evaluated body weight in the two groups of cats over time both as a surrogate marker of appetite and to assess whether Carnivora™ could induce any positive effect on body weight during stressful periods. In our model, body weight changes did not differ between the treatment and control groups. Most of the cats (94%; n=15/16) had a decrease in weight during the pre-inoculation treatment phase of the study. We suspect that the weight loss was due to the experience of stressors, including cage-housing, restraint, and multiple daily treatment administration events, in addition to hormonal and estrous related behaviors in the females. However, the amount of weight loss did not differ between the treatment and control groups in the pre-challenge or post-challenge periods, or overall. Carnivora™ did not contribute to weight loss to a greater extent than the control. However, the results also failed to show a positive effect of Carnivora™ on lessening stress associated weight loss or potential FHV-1 associated weight loss. A longer study or different model may be required to recognize this potential benefit of Carnivora™.

Clinical signs associated with FHV-1 were also detected in some cats in both groups during the pre-challenge, treatment period. It is likely that these clinical signs related to stress reactivation of FHV-1 accompanying the multiple daily administrations of either the treatment or placebo.<sup>35</sup> The cumulative clinical scores in this period were significantly less in those cats administered Carnivora™ which suggested a

treatment effect. Each owner and veterinarian should strategize the optimal way to administer Carnivora™ to avoid induction of stress.

## CONCLUSION

Overall, we conclude that this pilot study documented that Carnivora™ has immune modulating effects that can influence the course of FHV-1 infections in cats. The results should be confirmed in larger field studies, and future studies should evaluate the mechanisms of action and also establish bioavailability and pharmacokinetic parameters as bioavailability can be low for some of the metabolites in rodent models.<sup>36,37</sup> Further feline safety and efficacy studies with varied dosing regimens could also be considered.

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## DISCLOSURE STATEMENT

The study was sponsored by Carnivora™ but was performed in its entirety and masked to the scorers as described. Carnivora™ company representatives were not involved with data or analyses.

## FOOTNOTES

<sup>a</sup>Carnivora™; <http://www.carnivora.com/>

<sup>b</sup>Veterinary Diagnostic Laboratory, Colorado State University, Fort Collins, Colorado

<sup>c</sup>StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

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