applied sciences

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Dietary Supplemented Anthocyanin Reduced Serum Amyloid Beta Oligomers and Improved Cognitive Dysfunction Scores in Elderly Dogs

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Abstract: Like humans, the accumulation of amyloid-beta oligomers in the brains of aged dogs leads to cognitive dysfunction. Our study investigated the effects of dietary flavonoids in pet foods on cognitive dysfunction. All nine dogs (six species) recruited were older than seven years, and cognitive function was measured using a questionnaire before and after applying pet food containing *cyanidin-3-O-glucoside*, the main component of honeyberries. Physical examination, blood tests, cognitive dysfunction scores, and serum amyloid-beta oligomers were measured. After 90 days of pet food administration, a physical examination revealed no abnormalities in weight, body temperature, heart rate, or respiratory rate. However, the cognitive dysfunction score and serum amyloid-beta oligomers (AβO) marker levels were significantly reduced after 90 days. Inflammation and antioxidant levels were slightly, but not significantly, changed. Our results suggest that pet food containing anthocyanins effectively improves cognitive dysfunction scores and decreases serum AβO levels.

Keywords: pet food; *cyanidin-3-O-glucoside*; cognitive dysfunction score; serum AβO

Citation: Lee, M.-J.; Park, M.; Lee, H.-J. Dietary Supplemented Anthocyanin Reduced Serum Amyloid Beta Oligomers and Improved Cognitive Dysfunction Scores in Elderly Dogs. *Appl. Sci.* **2022**, *12*, 12130. https://doi.org/10.3390/app122312130

Academic Editor: Franco Mutinelli

Received: 7 November 2022
Accepted: 25 November 2022
Published: 27 November 2022

1. Introduction

As we age, we experience a complex aging process owing to accumulated cellular damage [1], such as various physical [2], cognitive [3], and emotional changes [4]. This leads to a gradual decline in physical and mental abilities [5]. Similarly, aging in dogs leads to changes in learning, memory, attention, administrative control, and social responses and decreased curiosity regarding new things. As dogs age, they develop neurogenic diseases called canine cognitive dysfunction (CCD). CCD or canine dementia affects up to 60% of older dogs, mostly those dogs older than 11 years [6]. Studies of neurodegenerative diseases in animals have revealed strong similarities between cognitive dysfunction in dogs and human Alzheimer's disease (AD) and between AD in humans and most other primates [7–11]. The causes of age-related neurodegenerative diseases are complex and diverse; however, the formation of aggregates of toxic proteins hinders the function of nerve cells, leading to final tissue removal [12].

We cannot overlook the importance of daily feed, given that diseased dogs generally have different nutritional requirements than healthy dogs. A number of studies and systematic reviews, including flavonoid components of berries [13–15], vitamin B [16], vitamin E [17], and vitamin B12 [18] in food and exercise training [19,20], have supported improvement in cognitive function. In this study, we examined the efficacy of flavonoid ingredients added to pet food in preventing CCD. Existing studies have mainly been conducted on humans. However, to our knowledge, this is the first study to investigate the function of flavonoids added to pet food for CCD research.

2. Materials and Methods

This study was conducted after obtaining informed consent and verbally explaining the necessity and method of the study and possible problems to the dog owners. This study was approved by the Laboratory Animal Ethics Committee (IACUC) (PTB-2021-IACUC-012-A). Among the candidate dogs, dogs were evaluated by their cognitive impairment behavioral scores with the consent of their guardians and were assessed through the behavioral questionnaire. Individuals with suspected neurological problems were excluded through physical and blood tests. The early behavioral diagnostic indicators of nine dogs were measured using a questionnaire. The comparison items before and after the application of pet food to prevent cognitive dysfunction were as follows: measurement of physical examination (body weight, body temperature, heart rate, and respiration rate), blood tests (CBC, chemistry, electrolyte), CDS, and serum indexes (anti-inflammatory and antioxidative indexes, AβO).

2.1. Animal Signalment

The signalment information of breed, sex, age, and body weight of the nine dogs are presented in Table S1. Classified by breed, six species were recruited. Five neutered males and four neutered females were recruited. All nine dogs were recruited only at seven years or older and their body weight varied from small breed (3.96 kg) to large species (28.00 kg).

2.2. Information on Cognitive Dysfunction Preventive Pet Food and Animal Maintenance

The nutrition for cognitive dysfunction prevention pet food developed by Erebon Co. (Erebon, Icheon, Republic of Korea) for this study is shown in Table 1. The main ingredients were oat, hydrolyzed chicken, chicken fat, beet pulp, fish oil, and hydrolyzed honeyberry. Moreover, chicken, the main protein component, and honeyberry, which helps improve cognitive function, were hydrolyzed to enhance digestion and absorption. As obtained in a previous mouse experiment, the honeyberries used in this study were determined by the amount of *cyanidin-3-O-glucoside* (C3G, Table 1), which is the main component of honeyberries [21,22]. Unlike in the mouse experiment, hydrolyzed honeyberry was used. Therefore, the value obtained through the analysis institution (Korea Health Supplement Institute, Republic of Korea) was converted and applied to the amount of pet food. Moreover, this pet food contained nutrients suitable for the dog's main food and was prepared in the form of extrusion, a general form. All dogs were fed individually for one day according to their weight (Table 1) at the feeding in the morning for 12 weeks, according to the instruction of the veterinarian. Food intake and the number of snacks were counted through counseling over the phone at least once a week, and at least four times, animal hospitals were required to visit for weight and blood collection.

Table 1. Information on nutrition on pet food for cognitive dysfunction prevention for this study.

Nutrition	Per Pet Food 100 g
Protein	24.43 g
Fat	13.53 g
Carbohydrate (NFE)	46.81 g
Calcium	1.20 g
Phosphorus	0.83 g
Sodium	0.40 g
Magnesium	0.13 g
Omega 6	2.61 g
Omega 3	0.95 g
L-carnitine	30.00 mg
Vitamin E	75.00 mg
Taurine	0.30 g
Cyanidin-3-glucoside (from honeyberry)	10.50 mg
Metabolizable energy	364.30 kcal

2.3. General Blood Test

Blood samples collected from individuals were separated from the serum, and CBC analysis was performed immediately. In the case of serum chemistry, if it was difficult to analyze directly, it was stored at −80 °C until the test. The CBC analysis equipment (XN-1000, Sysmex Corporation, Japan) and chemistry and electrolyte analysis equipment (BS-490, Mindray, China) were used according to the manufacturer's instructions.

2.4. CDS

Pan et al. [23] developed a behavioral diagnostic index questionnaire and evaluated the cognitive function accordingly.

2.5. Serum Anti-Inflammatory and Antioxidative Indexes

Canine blood samples were collected by a veterinarian, centrifuged, and analyzed according to the test method of each manufacturer. For the anti-inflammatory, we used canine IL-6 ELISA (#CSB-E11260c, Cusabio, Houston, TX, USA), canine IL-1β ELISA (#CSB-E13836c, Cusabio, Houston, TX, USA), and canine TNF-α ELISA (#ab193687, Abcam, Waltham, MA, USA). For the anti-oxidative assay, we used CRP (BS-490, Mindray, Beijing, China), GR assay (#ab83461, Abcam, Waltham, MA, USA), and carnitine quantification assay (#83392, Abcam, Waltham, MA, USA).

2.6. Serum AβO

Serum AβO as a biomarker related to cognitive dysfunction was measured using Absol HS equipment (Absology Co., Ltd., Dusseldorf, Germany) in the following experimental method according to the manufacturer's instructions. First, the samples, cartridges, and reagents were maintained at room temperature for approximately 20 min. Three reagents, 110 µL enhancer solution, 110 µL stable peroxide solution, and 2.2 µL ADHP concentrate were added to an Eppendorf tube, vortexed, and spun down. The mixed solution (100 µL) was placed into wells 7 and 8 of the prepared cartridge, 20 µL of the prepared serum was placed into well 1, and pipetting was performed approximately 10 times. This was then placed in the analysis equipment.

2.7. Statistical Analysis

Statistical analysis of the data was performed using the GraphPad Prism (version 9, GraphPad Software Inc., La Jolla, CA, USA) with a paired t-test and is presented as mean ± SD. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Physical Examination

Nine elderly dogs were evaluated. The results of the fundamental physical examinations are presented in Table 2. During the physical inspection, no abnormal findings were observed in body weight, body temperature, heart rate, or respiration rate, and no significant differences were observed on day 90 (Table 2).

Table 2. Physical examination results of 9 dogs that participated in clinical efficacy evaluation with cognitive dysfunction prevention pet food.

Items (Unit)	Day 0	Day 90
Body weight (Kg)	9.89 ± 9.49	9.85 ± 9.38
Body temperature (°C)	38.80 ± 0.35	38.59 ± 0.31
Heart rate (per minute)	124.44 ± 7.06	127.11 ± 5.93
Respiration rate (per minute)	31.11 ± 8.01	28.44 ± 5.64

Mean ± standard deviation.

3.2. Complete Blood Count (CBC), Chemistry, and Electrolyte

The complete blood count (CBC), chemical, and electrolyte analysis results are presented in Table 3. The CBC results showed no problems with suspected diseases (e.g., kidney disease, liver disease). The results were within the reference range, and no significant difference was observed on day 90. Serum chemistry and electrolyte analyses indicated no diseases of the kidney or liver, which could have caused neurological issues. Some increases in hepatobiliary values (ALT and ALP) were confirmed; however, these were believed to be changes in blood levels that could occur in older dogs (Table 3).

Table 3. Results of complete blood count (CBC), chemistry, and electrolytes of 9 dogs that participated in the clinical efficacy evaluation with cognitive dysfunction prevention pet food.

Category	Items (Unit)	Day 0	Day 90	Reference
CBC	WBC (10^9/L)	9.01 ± 3.54	7.92 ± 2.95	5.05–16.76
	RBC (10^{12}/L)	6.53 ± 0.74	6.52 ± 0.97	5.65–8.87
	HGB (g/dL)	14.36 ± 1.74	14.66 ± 2.47	13.1–20.5
	PCV (%)	44.70 ± 5.35	43.41 ± 6.82	37.1–65.0
	MCV (fL)	68.30 ± 2.74	66.74 ± 2.88	61.6–73.5
	MCH (pg)	21.93 ± 1.40	20.70 ± 5.26	21.2–25.9
	MCHC (g/dL)	32.08 ± 1.67	33.90 ± 3.26	32.0–37.9
	PLT (10^3/μL)	365.33 ± 124.18	388.38 ± 141.18	148–484
Chemistry	AST (U/dL)	24.71 ± 7.76	25.86 ± 8.93	15–43
	ALT (U/dL)	63.56 ± 34.96	84.50 ± 50.68	19–70
	ALP (U/dL)	205.11 ± 301.53	208.88 ± 396.89	15.0–127.0
	BUN (mg/dL)	18.68 ± 4.05	19.44 ± 9.24	8–26
	CRE (mg/dL)	0.87 ± 0.23	0.84 ± 0.27	0.5–1.3
Electrolytes	Na (mmol/L)	148.44 ± 6.21	142.88 ± 11.37	144–154
	K (mmol/L)	4.73 ± 0.81	4.24 ± 0.58	4.1–5.3
	Cl (mmol/L)	95.99 ± 42.57	113.50 ± 3.02	105.0–116.0

Mean ± standard deviation. WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; PCV, packed cell volume; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CRE, creatinine; Na, Natrium; K, potassium; Cl, chloride.

3.3. Cognitive Dysfunction Score (CDS)

The dogs were scored for cognitive dysfunction behavioral assessment using the corresponding behavioral questionnaire, and the average results are shown in Figure 1a. The score of the nine dogs varied from mild (1–29 points) to severe (30 issues or more) on day 0. However, all dogs showed an improvement in behavioral scores on day 90 compared with day 0. A significant difference was observed in the CDS evaluation ($p < 0.01$).

3.4. Serum Amyloid-Beta Oligomers (AβO)

Serum AβO, a biomarker related to cognitive dysfunction, was measured. The results are shown in Figure 1b and . The values of AβO were dramatically decreased on day 90 compared to day 0, except for one dog (dog no. 9). A significant difference was observed on day 90 compared with that on day 0 ($p < 0.05$).

3.5. Anti-Inflammatory and Antioxidative Indices

The evaluation results of anti-inflammatory and antioxidative indices in the serum of nine dogs are shown in Figure 2. No index was significantly different on day 90 compared with its value on day 0. In the case of IL-1β (Figure 2a), IL-6 (Figure 2b), TNF-α (Figure 2c), and CRP (Figure 2d), which are known indicators of inflammation in the body, the values of these indices were decreased on day 90 compared to day 0. In the case of L-carnitine (Figure 2e) and GR activity (Figure 2f), which are indicators of antioxidative function in the body, the values of these indices were increased on day 90 compared to day 0.

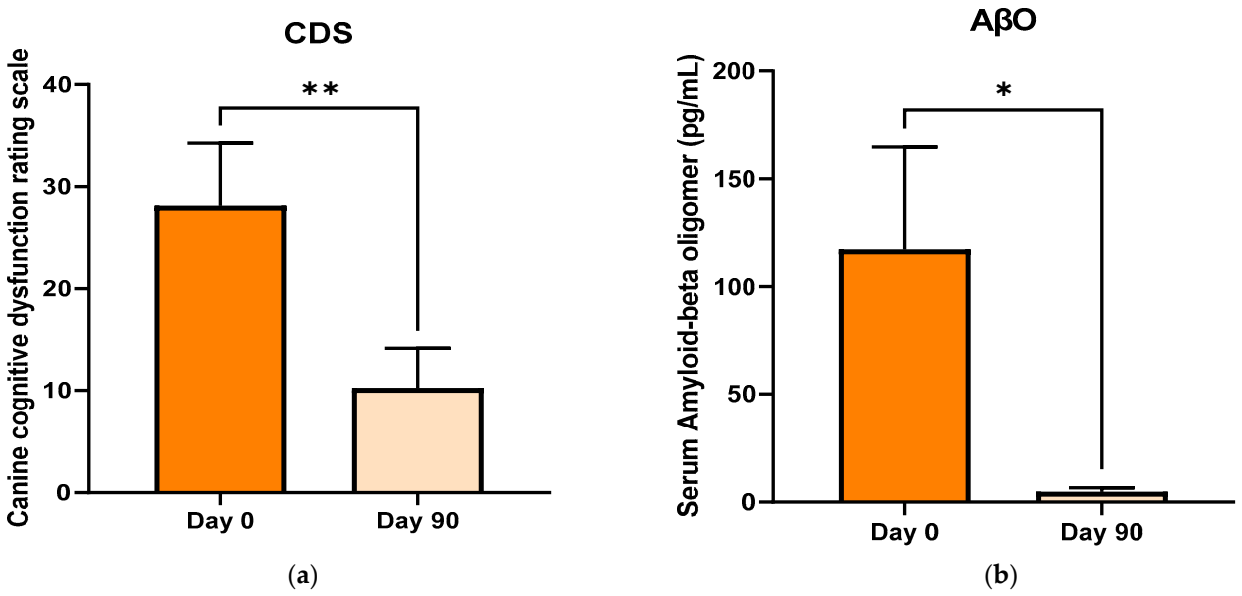

Figure 1. Results of 90 days after pet food containing anthocyanin for prevention cognitive dysfunction administered to elderly dogs. (**a**) Cognitive dysfunction score (CDS), (**b**) serum amyloid-beta oligomers (AβO). All data are presented as mean ± SE. * $p < 0.05$ and ** $p < 0.01$.

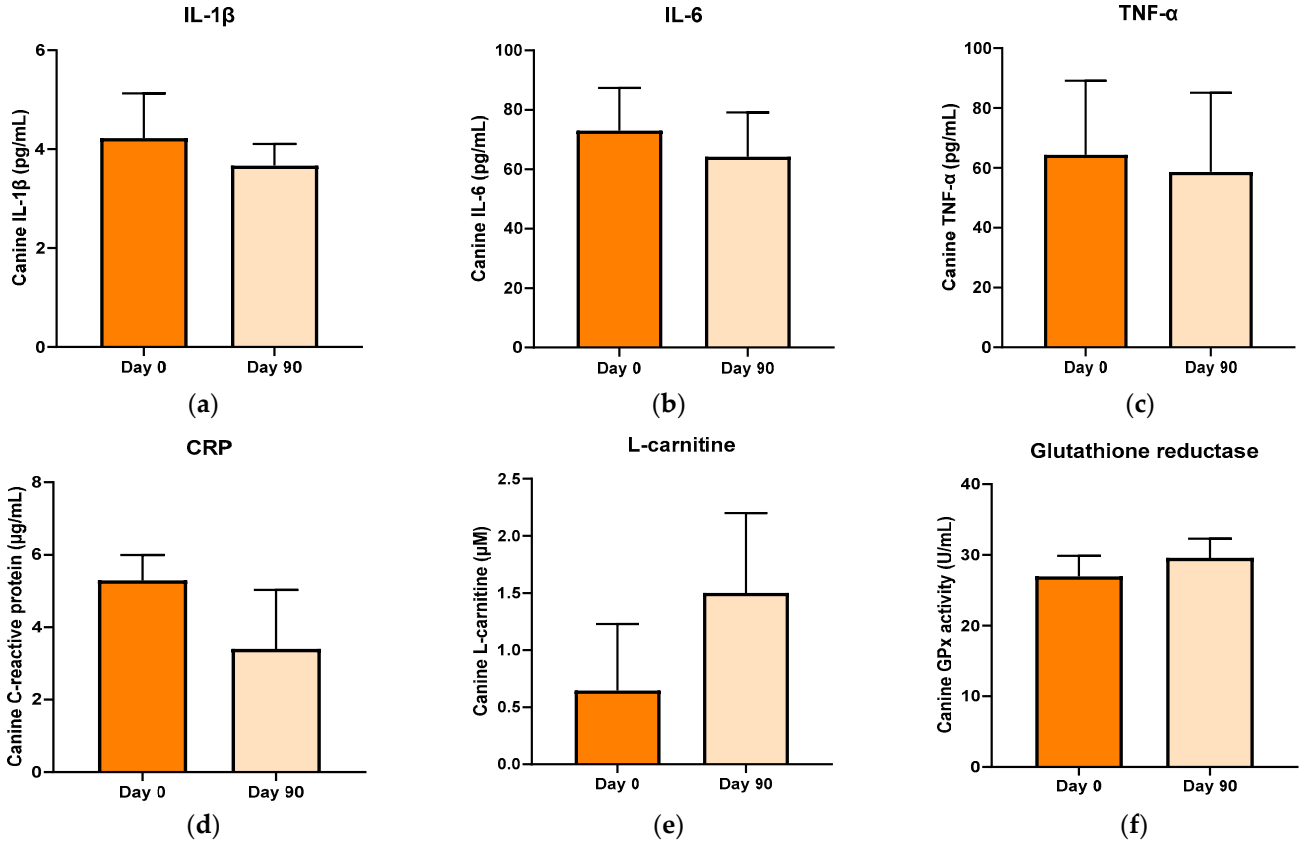

Figure 2. Results of anti-inflammatory and anti-oxidative indexes after 90days administration of pet food containing anthocyanin to elderly dogs: (**a**) IL-1β; interleukin 1 beta, (**b**) IL-6; interleukin 6, (**c**) TNF-α; tumor necrosis factor-alpha, (**d**) CRP; C-reactive protein, (**e**) L-carnitine, (**f**) GPx; glutathione reductase.

4. Discussion

This study confirmed the close relationship between serum AβO concentration and CDS in studies on the cognitive performance of elderly dogs. The serum AβO concentration could be lowered after 90 days by adding the flavonoid component C3G to pet food. Despite the small sample size, it demonstrated a significance of $p < 0.5$, and the blood levels of inflammatory markers also tended to decrease, though this decrease was not statistically significant. After 90 days of C3G treatment, antioxidant levels marginally increased but not significantly.

AβO causes neuronal cell death and cognitive impairment similar to AD, but it might take years or even decades for signs of AD to appear [24,25]. Targeting AβO is a crucial AD therapeutic strategy, and several medications are currently undergoing clinical trials to lower AβO. The topic of anti-AβO antibody treatment is still being debated. According to clinical trials, removing tau tangles and slowing cognitive decline in AD can be accomplished by employing antibodies to eliminate brain Aβ plaques [26]. Delaying the progression of AD by reducing the neuro-inflammatory response can also demonstrably lessen the severity of cognitive impairment [27].

Polyphenols have demonstrated anti-inflammatory properties and have been helpful in the treatment of a number of diseases [28]. In addition to their antioxidant properties, the actions of these natural compounds help control the expression of multiple inflammatory genes [29,30]. Our findings may support the neuroprotective effect of dietary anthocyanin in the central nervous system in elderly companion dogs [31], given that C3G can downgrade the expression of inflammatory cytokines in the brain cortex region of APPswe/PSEN1dE9 mice [22].

The study was limited by the amount of work required due to the relatively small number of dogs, the variety of species, and the requirement for the guardians to have prior training. Nevertheless, a larger experimental sample size may indicate significant anti-inflammatory and antioxidant results, given that the serum AβO and CDS values after 90 days of treatment were significantly decreased. Our findings imply that pet foods with effective antioxidants can lower serum AβO levels and enhance cognitive function in elderly dogs.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/app122312130/s1, Figure S1; The results of serum amyloid-beta oligomers (AβO) of 9 dogs administrated with pet food containing anthocyanin. Table S1; Signalment of 9 dogs that participated in clinical efficacy evaluation with cognitive dysfunction prevention pet food.

Author Contributions: Investigation and data arrangement, M.-J.L. and M.P.; writing and original draft preparation, M.-J.L. and M.P.; review and editing, H.-J.L.; conceptualization and supervision, M.P., and H.-J.L. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the "Cooperative Research Program of the Center for Companion Animal Research (Project No. PJ01476703)", Rural Development Administration, Republic of Korea.

Institutional Review Board Statement: This study was approved by the Laboratory Animal Ethics Committee (IACUC) (PTB-2021-IACUC-012-A).

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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