



# Evaluation of Clinical Efficacy and Safety Following Kyungokgo-Gamibang Administration in Dogs with Skin and Joint Diseases

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**Abstract** Skin and joint diseases are relatively common in dogs. Nutritional complementation is one of the various management strategies for these disorders. This study evaluated the safety and clinical efficacy of Kyungokgo-gamibang in dogs with skin and joint diseases. Thirty dogs with diseases were included and divided into three groups: control group (n = 15), skin group (n = 10), and joint group (n = 5). The skin and joint groups were fed skin and joint gums composed of Kyungokgo-gamibang extract with standard treatment for four weeks. The control group included dogs with skin diseases who were administered standard skin infection treatment for 4 weeks. The physical and laboratory results showed no remarkable adverse effects of Kyungokgo-gamibang extract after its administration in dogs. Clinical efficacy was evaluated using quality of life scale, and levels of cytokines, including interferon- $\gamma$ , interleukin (IL)-2, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1, and tumor necrosis factor- $\alpha$ , for 4 weeks in all groups. Dermatologic clinical scales were performed for 4 weeks in the control and skin groups. Both the control and skin groups had significantly decreased dermatologic clinical scales, including pruritus and erythema scales ( $p < 0.05$ ). Among the cytokine levels, only IL-2 concentration was significantly decreased in the skin group after 4 weeks of administration of the Kyungokgo-gamibang extract ( $p = 0.032$ ). There was no significant difference between the levels of cytokines on days 0 and 28 in the joint group. The quality of life scale was significantly increased after week 4 compared to week 0 in the skin ( $p = 0.008$ ) and joint groups ( $p = 0.041$ ). This study suggests that Kyungokgo-gamibang extract can be applied in managing dogs affected by skin and joint diseases without adverse effects.

**Key words** canine, Kyungokgo-gamibang, skin disease, joint disease, herbal medicine.

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## Introduction

Dermatologic diseases in companion animals are highly related to their overall health (1). Canine dermatologic disease is common in fold-skin, hypersensitivity disease, endocrine disease, and cornification defects (4). A common clinical symptom of skin diseases is pruritus, which can be caused by a hypersensitivity reaction, infectious dermatosis, or systemic disease (1). Treatment plans for skin diseases in dogs are difficult owing to the complexity of treatment (18).

Canine arthropathy can be classified into non-inflammatory and inflammatory joint diseases, also known as arthritis (15). Among various joint diseases, there is no cure for arthritis in dogs; therefore, a symptomatic treatment that relieves common symptoms by applying anti-inflammatory agents is followed (11). The incidence rate of musculoskeletal disease in dogs is 24%, of which 70% is related to the appendicular skeleton (16). Dogs with joint disease have common clinical symptoms, such as chronic pain and lameness, resulting in loss of joint function and mobility, ultimately reducing the quality of life (11).

Kyungokgo, which is composed of the root of ginseng, *Poria cocos*, the root of *Rehmanniae*, and honey, is a traditional Korean herbal composition that has various physiologic effects such as modulation of the immune system and improvement of memory (8,19). Kyungokgo has been used to control general weakness in traditional medicine (6). Kyungokgo-gamibang consists of Kyungokgo ingredients, *iksuyongjingo*, and *sparassis crispa* (12). Several studies have reported that Kyungokgo-gamibang significantly improves antioxidant activity and immune-modulating effects (7,12). Moreover, a previous experimental study reported that Kyungokgo improved hypertension, hyperglycemia, fatigue, and body weight loss in mice (21). However, few studies on the clinical effects of Kyungokgo-gamibang on various diseases, including canine skin and joint diseases, have been conducted in veterinary medicine. This study aimed to verify the safety and clinical efficacy of Kyungokgo-gamibang extract in dogs with skin and joint diseases.

## Materials and Methods

### Test compound

Two types of gums based on Kyungokgo-gamibang extract were used in this experiment. The basic materials of Kyungokgo-gamibang extract are as follows: rice flour (52-56%), cellulose (8-11%), hydrolyzed salmon (4-7%), refined glucose (2-4%), SHMP (0.5-1%), potassium sorbate (0.5-1%), spirulina (0.5-1%), beta-glucan (0.01-0.05%), glucosamine

(0.01-0.05%), marigold extract powder (0.01-0.05%), fish oil powder (0.01-0.05%), blueberry powder (0.01-0.05%), yucca extract (0.01-0.05%), fucoidan (0.01-0.05%), L-arginine (0.01-0.05%), propolis (0.01-0.05%), fructooligosaccharides (0.01-0.05%), mannan oligosaccharide (0.01-0.05%), psyllium husk (0.01-0.05%), vitamin complex (0.01-0.05%), mineral mixture (0.01-0.05%), amino acid mixture (0.01-0.05%), glycerin (6-9%), propylene glycol (4-7%), sorbitol (2-4%), and water (3-6%). Gums for immune and skin diseases are additionally formulated using ingredients including flaxseed (0.5-1.0%), collagen (0.01-0.05%), and hyaluronic acid (0.01-0.05%). Gums for immune and joint diseases are additionally formulated using ingredients including MSM (0.01-0.05%), green lipped mussel powder (0.01-0.05%), and chondroitin (0.01-0.05%) as compounding agents.

### Animals and study design

This study assessed the efficacy of Kyungokgo-gamibang extract as a supplement in dogs with skin and joint diseases. Twenty-five dogs with skin diseases and five with joint diseases were enrolled, with the owners' consent. All procedures were approved by the Institutional Animal Care and Use Committee (PTB-2021-IACUC-014-A). Twenty-five dogs with skin diseases were randomly divided into two groups: a control group (n = 15) and a skin group (n = 10). The control group was given standard treatment for skin infections, and the skin group was given gums for immune and skin diseases along with standard treatment for 4 weeks. Standard treatment included antibiotics including cephalexin and metronidazole with shampoo of 2% chlorhexidine gluconate and 2% miconazole nitrate. Five dogs with joint disease were selected as the joint group and fed gums for immune and joint diseases for 4 weeks. The skin and joint groups were fed 1-2 gums every day for 4 weeks. All 25 dogs in the control and skin groups were diagnosed with infectious dermatitis caused by *Malassezia spp.* The joint group included dogs with hip dysplasia (grade 1; n = 2) or patellar luxation (grade 2; n = 3). The efficacy of the gums for immune and skin disease was evaluated at 0 and 4 weeks after the first administration using pruritus and erythema scales. The efficacy of the gums for the immune and joint disease was evaluated at 0 and 4 weeks after the first administration based on cytokine levels. The safety of the two types of gums was evaluated by physical and laboratory examinations, including complete blood count (CBC) and serum chemistry, at 0 and 4 weeks after the first administration.

### Physical and laboratory examination

Physical examination included heart rate (HR), body tem-

perature (BT), and respiratory rate (RR) of all dogs 0 and 4 weeks after the first administration. In addition, laboratory examinations were performed, including CBC analysis (XN-1000; Sysmex, Kobe, Japan) and serum chemistry profiles (BS-490; Mindray, Shenzhen, China) in all dogs at 0 and 4 weeks after the first administration. CBC evaluation included white blood cell count, red blood cell count, hemoglobin level, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and platelet count. Serum chemistry profiles included blood urea nitrogen, creatinine, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total protein, and albumin levels.

### Serum cytokine concentrations

The cytokine concentrations, including interferon (IFN)- $\gamma$ , interleukin (IL)-2, IL-6, IL-8, IL-10, monocyte chemoattractant protein (MCP)-1, and tumor necrosis factor (TNF)- $\alpha$ , were analyzed in all groups using multiplex immunoassay (MILLIPLEX<sup>®</sup> Canine Cytokine/chemokine magnetic bead panel; CCYTOMAG 90 K; EMD Millipore, USA) at 0 and 4 weeks. Immunoassays were performed according to the manufacturer's instructions.

### Pruritus and erythema scale

Pruritus was assessed in the control and skin groups using a previously described method by the owners (14). In the case of a normal state with minor itching, it was evaluated using a scale of 0. If the dog showed pruritus and was mostly comfortable, it was evaluated on a scale of 1. If the dog did not itch much but the frequency of pruritus increased, it corresponded to a scale of 2. If the dog had severe pruritus and was often uncomfortable, it was evaluated on a scale of 4. If the dog experienced extreme pruritus and scratched continuously, the pruritus scale was evaluated at five points. The erythema scale was assessed according to the 0-3 Otitis Index Score (OTIS3) for erythema by the veterinarians (13). The erythema scale ranged from no erythema (scale 0) to the most severe erythema (scale 3) in each dog.

### Quality of life (QoL) scale

QoL was assessed in all groups using the HHHHHMM QoL scale (20). The HHHHHMM scale is an abbreviation of the sum score of hurt, hunger, hydration, hygiene, happiness, mobility, and more good days than bad days. Each value was scored from 0 points for the worst to 10 points for the best, and the total score was calculated for the control, skin, and joint groups at 0 and 4 weeks after the first administration.

### Statistical analysis

All continuous data were presented as mean  $\pm$  standard deviation. Statistical analyses were performed using SPSS version 20 (IBM, Chicago, IL, USA). The normality of all tested variables was assessed using the Kolmogorov-Smirnov analysis. Kruskal-Wallis and post-hoc tests were used to compare the results of the physical examination between the control, skin, and joint groups. Laboratory values before and after applying the Kyungokgo-gamibang extract were compared using the Mann-Whitney U test in each group. The comparison of variables for clinical efficacy before and after applying Kyungokgo-gamibang extract was performed using the Wilcoxon signed-rank test in each group. Statistical significance was set at  $p < 0.05$ .

## Results

### Baseline characteristics

Thirty dogs were included and classified into control, skin, and joint groups. The breeds in the control group included Chihuahua ( $n = 6$ ), Shih-tzu ( $n = 5$ ), Maltese ( $n = 1$ ), Papillion ( $n = 1$ ), Miniature Pinscher ( $n = 1$ ), and Yorkshire terrier ( $n = 1$ ). The breed distribution of the skin groups was as follows: Beagle ( $n = 4$ ), Cocker Spaniel ( $n = 3$ ), and Shetland Sheepdog ( $n = 3$ ). The joint group included only Cocker Spaniel ( $n = 5$ ). The control group included spayed females ( $n = 13$ ) and castrated males ( $n = 2$ ). The skin group included spayed females ( $n = 9$ ) and castrated males ( $n = 1$ ). The joint group included spayed females ( $n = 3$ ) and castrated males ( $n = 2$ ).

### Safety evaluation

Physical and laboratory examinations were performed in the control, skin, and joint groups to evaluate the safety of the Kyungokgo-gamibang extract at 0 and 4 weeks after the first administration. The HR, BT, and RR of all dogs at 0 and 4 weeks after the first administration were within the normal ranges, and there was no significant difference between the groups ( $p > 0.05$ ). On laboratory examination, there was no remarkable change in all groups in the CBC tests, and there was no significant difference between the variables on days 0 and 28 ( $p > 0.05$ ). In addition, the serum chemistry profile showed no significant difference between the variables on days 0 and 28 in the control and joint groups ( $p > 0.05$ ). In the skin group, only one variable, GGT (U/L; reference range, 0-6 U/L), significantly increased from  $4.8 \pm 0.8$  U/L to  $5.8 \pm 0.9$  U/L after administration ( $p = 0.035$ ); however, it was within the normal range.

## Evaluation of clinical efficacy

To evaluate the efficacy of the gums for immune and skin diseases, the erythema and pruritus scale scores were compared between day 0 and day 28 after administration in the control and skin groups. The control group had significantly decreased erythema ( $p < 0.001$ ) and pruritus ( $p < 0.001$ ) scales on day 28 compared to day 0 (Table 1). The skin group also had a significantly decreased erythema scale score ( $p =$

0.004) and pruritus scale score ( $p = 0.014$ ) on day 28 compared to day 0.

To evaluate changes in cytokines related to the immune mechanism of canine skin and joint diseases after administration of Kyungokgo-gamibang extract, cytokine levels including IFN- $\gamma$ , IL-2, IL-6, IL-8, IL-10, MCP-1, and TNF- $\alpha$  were assessed before and after the administration of the skin and joint gums. A significant decrease in IL-2 levels was observed in the skin group ( $p = 0.032$ ) (Table 2). However, no remarkable changes in the other cytokines were observed in the control, skin, and joint groups during the test period.

The QoL scale was evaluated in the control, skin, and joint

**Table 1. Erythema and pruritus scale before and after administration of Kyungokgo-gamibang extract in the control and skin groups**

Parameters	Group	D0	D28	p
Erythema scale	Control (n = 15)	1.3 $\pm$ 0.6	0.6 $\pm$ 0.7	<0.001**
	Skin (n = 10)	1.5 $\pm$ 0.5	0.5 $\pm$ 0.5	0.004**
Pruritus scale	Control (n = 15)	1.1 $\pm$ 0.8	0.3 $\pm$ 0.6	<0.001**
	Skin (n = 10)	1.4 $\pm$ 0.5	0.8 $\pm$ 0.8	0.014*

D, days after administration.

\* $p < 0.05$ . \*\* $p < 0.01$ .

**Table 3. Quality of life scale before and after administration of Kyungokgo-gamibang extract in the control, skin, and joint groups**

Parameter	Group	D0	D28	p
QoL scale	Control (n = 15)	59.7 $\pm$ 7.9	60.5 $\pm$ 6.4	0.242
	Skin (n = 10)	59.8 $\pm$ 5.9	63.7 $\pm$ 4.1	0.008**
	Joint (n = 5)	53.4 $\pm$ 8.2	58.6 $\pm$ 6.4	0.041*

D, days after administration; QoL, quality of life.

\* $p < 0.05$ . \*\* $p < 0.01$ .

**Table 2. Cytokine levels of 30 dogs before and after administration of Kyungokgo-gamibang extract**

Parameters	Group	D0	D28	p
IFN- $\gamma$ (pg/mL)	Control (n = 15)	109.0 $\pm$ 253.3	14.3 $\pm$ 28.7	0.147
	Skin (n = 10)	69.4 $\pm$ 208.6	1.4 $\pm$ 1.3	0.176
	Joint (n = 5)	24.6 $\pm$ 50.6	77.2 $\pm$ 147.3	0.893
IL-2 (pg/mL)	Control (n = 15)	97.0 $\pm$ 142.3	71.9 $\pm$ 90.9	0.570
	Skin (n = 10)	125.5 $\pm$ 138.8	23.2 $\pm$ 26.7	0.032*
	Joint (n = 5)	39.2 $\pm$ 53.2	85.2 $\pm$ 111.6	0.686
IL-6 (pg/mL)	Control (n = 15)	60.2 $\pm$ 67.4	70.3 $\pm$ 94.3	0.798
	Skin (n = 10)	62.2 $\pm$ 59.4	27.0 $\pm$ 29.8	0.241
	Joint (n = 5)	42.2 $\pm$ 48.2	89.8 $\pm$ 106.8	0.686
IL-8 (pg/mL)	Control (n = 15)	14850.0 $\pm$ 15148.4	7610.5 $\pm$ 7356.0	0.173
	Skin (n = 10)	6279.0 $\pm$ 6147.0	8344.3 $\pm$ 5462.5	0.386
	Joint (n = 5)	11133.8 $\pm$ 6778.1	9733.2 $\pm$ 5791.5	0.500
IL-10 (pg/mL)	Control (n = 15)	98.7 $\pm$ 202.9	148.9 $\pm$ 330.2	0.576
	Skin (n = 10)	226.5 $\pm$ 479.8	19.8 $\pm$ 13.1	0.213
	Joint (n = 5)	79.6 $\pm$ 87.3	313.0 $\pm$ 486.8	0.686
MCP-1 (pg/mL)	Control (n = 15)	553.8 $\pm$ 208.2	512.7 $\pm$ 452.3	0.570
	Skin (n = 10)	461.9 $\pm$ 274.0	374.1 $\pm$ 143.4	0.333
	Joint (n = 5)	359.2 $\pm$ 179.0	536.0 $\pm$ 375.6	0.686
TNF- $\alpha$ (pg/mL)	Control (n = 15)	25.3 $\pm$ 41.4	53.3 $\pm$ 95.5	0.529
	Skin (n = 10)	37.4 $\pm$ 53.2	5.2 $\pm$ 12.7	0.441
	Joint (n = 5)	16.8 $\pm$ 34.2	57.2 $\pm$ 93.3	0.893

D, days after administration; IFN- $\gamma$ , interferon-gamma; IL, interleukin; MCP, monocyte chemoattractant protein; TNF- $\alpha$ , tumor necrosis factor-alpha.

\* $p < 0.05$ .

groups before and after the administration of Kyungokgo-gamibang extract. In the control group, no significant difference in the QoL scale was observed before and after the administration, but the QoL scale was significantly increased in the skin group ( $p = 0.008$ ) and the joint group ( $p = 0.041$ ) (Table 3). The skin group had a tendency to increase of scores of hygiene and more good days than bad days, while the joint group had a tendency to increase of mobility and more good days than bad days after the administration.

## Discussion

This study demonstrated that consuming both skin and joint snacks containing Kyungokgo-gamibang extract produced improvement of QoL in dogs with skin and joint diseases. Dogs affected by skin and joint diseases who were administered the Kyungokgo-gamibang extract had significantly improved QoL compared with dogs who hadn't been administered the same. A previous study showed that Kyungokgo induced the proliferation of osteoblasts and reduced bone loss *in vivo* (6). Although the exact mechanism of action of Kyungokgo-gamibang extract for clinical improvement is unknown, considering the fact that Kyungokgo-gamibang extract has beneficial anti-inflammatory and antioxidant effects (7,12), it is believed that nutritional supplements composed of Kyungokgo-gamibang extract led to improvement of QoL in dogs with skin and joint disease in this study. Because skin and joint diseases require complex and long-term treatment, including oral, injection, and topical application methods (18), nutritional supplements could be helpful in managing dogs with these diseases. Moreover, in the case of canine joint disease, the use of nonsteroidal anti-inflammatory drugs may be associated with detrimental effects, especially gastrointestinal adverse effects (11). Therefore, alternative treatments are desirable, and various nutraceuticals are known to be effective in several canine skin and joint diseases (10,11). Considering the results of this study, Kyungokgo-gamibang extract could have beneficial effects on clinical improvement in the management of canine skin and joint diseases.

Despite many reports on the adverse effects of herbal medicine in animals (2), no adverse effects were observed after the administration of Kyungokgo-gamibang extract in this study. All dogs in this study showed no adverse effects, without abnormal changes in laboratory profiles before and after administration of Kyungokgo-gamibang extract. Similar results were reported that Kyungokgo-gamibang extract could be safely used in dogs, as proven by single-dose and repeated-dose oral toxicity studies (17). Kyungokgo has

been used for a long time in humans, and its physiologic side effects on animals might be different from those of humans considering species-based factors (2), but it seems that Kyungokgo-gamibang extract could be administered in dogs without any specific side effects from the results of this study.

This study revealed a significant decrease in IL-2 levels in the skin group after the administration of Kyungokgo-gamibang extract. IL-2 is involved in important immunologic functions, such as the activation and regulation of inflammatory responses (5). IL-2, a 15 kDa cytokine, is mainly secreted by activated T cells and stimulates the proliferation of lymphocytes, macrophages, and natural killer cells (3,9). Therefore, considering the improvement of clinical symptoms of dermatologic diseases, including pruritus and erythema, along with the reduction of IL-2, Kyungokgo-gamibang extract is considered a nutritional supplement that helps improve clinical signs by regulating the inflammatory response in canine skin disease.

This study had several limitations. First, it was difficult to confirm the single effect of Kyungokgo-gamibang extract because the clinical efficacy was evaluated using standard treatment in combination with the administration of Kyungokgo-gamibang extract in dogs with skin and joint diseases. Although the potential benefits of the standard therapy might also have affected the efficacy evaluation, the administration group, including the skin and joint groups, showed significant clinical efficacy compared to the control group. In addition, the number of patients in each group was relatively small. Therefore, further large-scale research is needed to assess the long-term clinical efficacy and safety of Kyungokgo-gamibang extract.

This report describes the safety and clinical efficacy of nutritional supplements composed of Kyungokgo-gamibang extract for canine skin and joint diseases. No remarkable adverse effects were observed after the administration of Kyungokgo-gamibang extract, indicating that the complement was well tolerated. Furthermore, clinical efficacy was validated by evaluating the dermatologic clinical scale, cytokine levels, and QoL scale. Therefore, Kyungokgo-gamibang extract can be used as an adjunctive treatment for dogs with skin and joint diseases.

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## Conflicts of Interest

The authors have no conflicting interests.

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