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**PANTOEA AGGLOMERANS LPS SUPPLEMENT: A NEW
APPROACH TO PREVENT CANINE ALLERGIC DERMATITIS**

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ABSTRACT

Although various methods are available for treating canine atopic dermatitis such as those employing steroids, interferon, or antibiotics, as well as human treatments, treatments without detrimental side effects are still needed. We screened a safe treatment method and found that oral administration of *Pantoea agglomerans*-derived lipopolysaccharide (LPS) from wheat flour controlled host immune conditions. This Gram-negative bacterium exists in various edible plants. Oral administration of this LPS enhances macrophage phagocytic activity in mice and fish. In the mouse model, LPS activates macrophages through Toll like receptor (TLR)-4. We prepared an LPS-containing supplement for dogs with atopic dermatitis. In a preliminary experiment, 24 dogs with atopic dermatitis were administered the LPS supplement, and a 62.5% improvement was observed. These results indicated that *Pantoea agglomerans* LPS supplement is a fruitful candidate for canine atopic dermatitis.

Atopic dermatitis and the hygiene hypothesis

Many agents cause canine atopic dermatitis, such as fleas, house dust, and food. Approximately 20%–30% of dogs suffer from atopic dermatitis in Japan. The major reasons for atopic dermatitis are genetic factors as well as environmental circumstances. Shiba, Shih Tzu, Golden retriever, and Labrador Retriever breeds are sensitive to atopic dermatitis. The hygiene hypothesis focuses on the environmental factors associated with human allergic diseases. Mutius *et al.* suggested that an increase in hygienic management results in an increase in allergies because of a decrease in the

number of exposure opportunities, the dose of Gram-negative bacteria, and lipopolysaccharide (LPS, endotoxin)¹⁾. The modern hygienic lifestyle appears to supply insufficient Gram-negative bacteria and/or LPS. LPS promotes the release of proinflammatory cytokines such as interleukin-12 (IL-12) and tumor necrosis factor in macrophage culture and animal body, and this has caused a shift in the Th2 dominant immune balance, resulting in the spread of allergic diseases.

LPS as a functional food material

We unconsciously consume a significant amount of LPS in some foods, as LPS occurs widely in commercially available foods such as vegetable powders, health foods, and Chinese medicines, and sometimes, in quite large amounts (0.16–600 g/g)²⁾. For example, fermented rye bread, which is a popular health food in the EU and US, is made from sour dough by fermentation with *Pantoea agglomerans* and *Lactobacillus*. *Pantoea agglomerans* is Gram-negative bacterium and a concomitant bacterium present on various edible plants and proliferates during the beginning of rye bread fermentation.

We have developed the processing method to obtain an immunopotentiator from the edible Gram-negative bacteria, *P. agglomerans*, LPS. *P. agglomerans* fixes nitrogen and inorganic phosphorus and is symbiotic in nature in various plants such as rice, sweet potato, apple, and pear. In Europe, viable *P. agglomerans* has been developed as a biological control for post-harvest pome fruit diseases. These observations demonstrate that *P. agglomerans* has a long history of being consumed in foods with apparent safety. In fact, oral administration of *P. agglomerans*-derived LPS does not result in toxicity in animal safety evaluations³⁾.

Preventive effect of *P. agglomerans*-derived LPS on canine atopic dermatitis

We used a supplement tablets (5 mm diameter and 3 mm height, supplied by Scarecrow Inc, Japan), which contained LPS as an extract of *P. agglomerans*-fermented wheat flour. Twenty-four dogs (mean age, 6.1 ± 3.4 years), which were diagnosed with atopic dermatitis or allergic dermatitis (based on medical records, cutis symptoms, and International Task Force on Canine Atopic Dermatitis diagnostic criteria), were registered for an open trial. Drug treatments were allowed to continue for dogs being treated with a drug. However, if a dog was receiving another supplement, the supplement was stopped. The dogs were administered the supplement tablets at 10–20 g/kg LPS body weight/day for 1–2 months in a standard meal or as a supplement by itself. Twenty-one dogs were being treated with drugs (steroids,

antihistamines, or antimicrobials) and three were not.

All dogs took the LPS supplement without a problem. It was possible to administer the supplement by mixing it with food, because the tablets were small. Of the 24 cases, 4 developed a significant response (two dogs received the supplement alone and two were supplemented in combination with a drug) (16.7%), 11 developed a minor response (one case involved a single administration, and 10 dogs were administered with a drug) (45.8%), and 7 did not change (all cases involved a drug combination) (29.1%). Thus, the total response rate was 62.5%. A temporary deterioration in cutis symptoms was observed in one case at 2 weeks after administration. The symptoms of this dog improved, but the cause was unknown. No decrease in quality of life was observed among the dogs.

DISCUSSION AND CONCLUSION

The hygienic hypothesis states that animals lived in an environment that was less hygienic in the past. Thus, they consumed larger amounts of bacteria and LPS. As modern hygienic life has led to a relatively low consumption of LPS, we proposed producing an LPS supplement that had immune-regulating functions and suppressed the generation of allergies. We believe that this new product can be used as a new health preparation and will help dispel the unwarranted toxic image of LPS. LPS induces IL-12, which is a predominant Th1 cytokine. Because of the currently followed highly hygienic lifestyle, Th1/Th2 immune balance is biased toward Th2 because of a lack of bacteria and exposure to LPS. In other words, LPS is considered necessary for maintaining the immune balance. Some researchers insist that LPS is not an endotoxin but an exogenous hormone⁴⁾.

LPS has a widely known effect of activating macrophages which play a central role in innate immunity. To clarify and establish LPS therapy for canine allergies other intractable diseases, we are investigating the anti-allergic effect of LPS by introducing biochemical and immunological criteria with cooperation from veterinarians.

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