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Preventive Effect of *Cladosiphon okamuranus*-Derived Fucoidan against Influenza Virus Infection via Dendritic Cell Activation

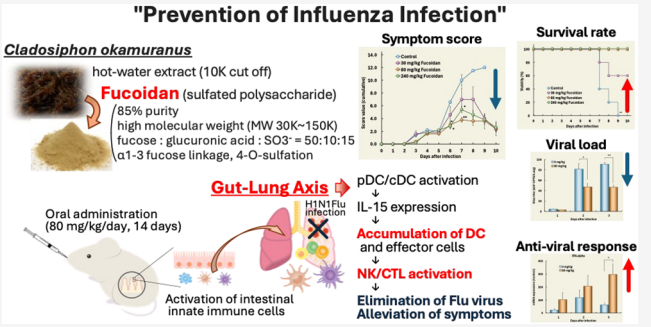
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ABSTRACT: Fucoidan is a sulfated polysaccharide contained in the viscous components covering the surface of brown algae. We previously revealed that fucoidan derived from *Cladosiphon okamuranus* (*C. okamuranus*) cooperatively activates innate immune cells upon stimulation with several pathogen components. Therefore, in this study, the preventive effect of fucoidan against viral infection was evaluated. BALB/c mice were continuously administered 30, 80, or 240 mg/kg of *C. okamuranus*-derived fucoidan intragastrically for 14 days, subsequently infected with the H1N1 influenza virus. In the control mice, the symptom scores rapidly increased from day 5 postinfection, and all mice died by day 9, whereas in the mice administered 80 mg/kg or more of fucoidan, the symptoms were ameliorated, and death associated with infection was prevented. Viral proliferation in the lungs was significantly suppressed with 80 mg/kg fucoidan during the 3 days postinfection. Furthermore, fucoidan induced an effective antiviral response, characterized by the upregulation of type I and II interferon expression and the accumulation of immune cells. These results clearly demonstrate the efficacy of fucoidan in preventing influenza infection.



KEYWORDS: *sulfated polysaccharide, fucoidan, influenza infection, immune activation, dendritic cell*

1. INTRODUCTION

Fucoidan is a type of natural sulfated polysaccharide that constitutes the sliminess of seaweed.[1] As a soluble dietary fiber, it has been reported to exert physiological effects that reduce risk factors for lifestyle-related diseases, such as suppressing blood glucose elevation and controlling blood lipid concentrations.[2] Additionally, it is known to contribute to the prevention of cancer and infectious diseases by interacting with tumor cells, pathogens, and proteins involved in their metastasis and host invasion.[3−5] However, fucoidan, an indigestible and poorly absorbable food component with a molecular weight ranging from tens to hundreds of thousands, reaches systemic circulation and local lesions via intestinal absorption in extremely limited amounts.[6] Thus, it is unlikely to directly act on cancer cells or pathogens in tissues and blood to exert the aforementioned physiological functions.

On the other hand, our previous study showed that *Cladosiphon okamuranus* (*C. okamuranus*)-derived fucoidan enhanced nitric oxide (NO) and tumor necrosis factor-α (TNF-α) production by interacting with the mouse macrophage-like cell line RAW264.[7] This suggests that bioactive polysaccharides, including fucoidan, contribute to the enhancement of systemic antitumor and infection immunity by stimulating the intestinal immune system, particularly innate immune cells such as dendritic cells and macrophages.[8,9]

Regarding viral infections, sulfated polysaccharides contained in seaweed possess potent physiological activities, such as inhibiting host invasion and suppressing the proliferation of pathogenic viruses (e.g., influenza, dengue fever, and human immunodeficiency virus), as well as enhancing infection immunity.[10] Among them, there are many reports on the antiviral activity of fucoidan, including its infection-inhibitory effects against the herpes simplex virus (HSV), human hepatitis B virus (HBV), adenovirus, and SARS-CoV-2.[11] Interestingly, it has been proposed that multiple pathways exist in fucoidan's mechanism of antiviral action, including direct antiviral actions—such as interactions with spike proteins that serve as scaffolds for host invasion and the inhibition of enzymes associated with viral replication—as well as the enhancement of the antiviral immune response, namely, viral clearance mediated by the induction of immune cell activation.[9,11]

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Table 1. Score Index on Symptom in Flu Infection

Score	Observation locus					
	(A) Eyelid	(B) Hair coat	(C) Behavior	(D) Respiration	(E) Rectal temp.	(F) Body weight
4	—	—	—	—	Hypothermia (decline > −4 °C)	Emaciation (decline > −30%)
3	Eyelid adhesion (close of eyelid)	Extreme worsen in hair coat	Lost of locomotion (not move with touch, abdominal/lay/dorsal decubitus position)	Respiratory failure	Decreased rectal temperature (3−4 °C)	Decreased body weight (25−30%)
2	Lost of eyelid reflex (open eyes with touch, but not blink)	Lost of hair sheen	Decrease of locomotion (move with touch)	Distinct respiration irregular	Decreased rectal temperature (2−3 °C)	Decreased body weight (20−25%)
1	Close eyelid (open with touch)	Piled hair	Interesting in ambient, responding to irritation	Respiration irregular (Tachypnea or bradypnea)	Decreased rectal temperature (1−2 °C)	Decreased body weight (10−20%)
0	Normal (shiny eye)	Normal (good hair coat)	Normal	Normal (not breathing disorder)	Normal	Normal

In addition, protective effects against influenza virus infection have been reported for fucoidan derived from *Undaria pinnatifida* (Wakame), *Sargassum fusiforme* (Hijiki), and *Kjellmaniella crassifolia* (Gagome). However, their mechanisms of action vary, encompassing the enhancement of virus-neutralizing antibody production, binding to HA proteins, and the inhibition of intracellular signaling pathways via the EGF receptor.[12−14] Considering that the structure of fucoidan (including its monosaccharide composition and glycosidic linkage patterns) varies depending on the species of seaweed from which it is derived,[15] it is crucial to investigate the antiviral effects and mechanisms of action for fucoidan from each specific seaweed species. Host defense responses to viral infection are regulated by dendritic cells, functioning through the coordination of plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs).[16−18] In this study, we verified the preventive effect of *C. okamuranus*-derived fucoidan against influenza virus infection and elucidated its underlying mechanism of action.

2. MATERIALS AND METHODS

2.1. Test Samples and Reagents

The fucoidan used in this study was a spray-dried powder produced through hot-water extraction under acidic conditions and ultrafiltration (<10 kDa cutoff) processes using *C. okamuranus* harvested in Okinawa Prefecture as a raw material; it was provided by the specified nonprofit corporation NPO Research Institute of Fucoidan (Fukuoka, Japan). The standard specifications for the test material are a molecular weight of 30,000 to 150,000 and a fucoidan purity of ≥ 85%. The H1N1 influenza virus (A/PR/8/34 strain) was obtained from the American Type Culture Collection (ATCC, VR-1469, Manassas, VA), and the inoculated virus stock solution—prepared using the canine kidney cell line MDCK (JCRB9029, Japanese Collection of Research Bioresources Cell Bank, Osaka, Japan) as host cells—was cryopreserved in an ultralow temperature freezer (controlled temperature: −90 to −70 °C, MDF-394, SANYO Electric Co., Ltd., Osaka, Japan) until use.

2.2. Animal Experiments

Animal infection studies were conducted at the Kiso-Sansen branch, Hashima Laboratory, Nihon Bioresearch Inc. (Gifu, Japan). The study protocol was prepared in accordance with the "Basic Guidelines for Conducting Animal Experiments in Implementing Agencies under the Jurisdiction of the Ministry of Health, Labour and Welfare" (Notification No. 0601001 of the Ministry of Health, Labour and Welfare, June 1, 2006), and was reviewed and approved by the Institutional Animal Care and Use Committee established at the animal experiment facility in accordance with the "Regulations on the Care and Welfare of Laboratory Animals at Nihon Bioresearch Inc." (April 2, 2007) (Study No. 430270, Gifu, Japan). For animal experiments, 4-week-old female BALB/c CrSlc mice were purchased from Japan SLC, Inc. (Shizuoka, Japan), individually acclimatized for 4 or 6 days (cage size: W175 x D245 x H125) using a solid diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) (controlled room temperature: 18−28 °C, 12-h light/dark cycle (lighting: 6:00 to 18:00)), and then divided into groups (n = 5) so that the mean body weight and its variance were approximately equal. The test sample fucoidan powder was dissolved in Water for Injection (WFI, Otsuka Pharmaceutical Factory Inc., Tokushima, Japan) to 60 mg/mL, and administered intragastrically by forced oral gavage using a metal oral sonde for mice (Fuchigami Instruments Ltd., Kyoto, Japan) at doses of 30, 80, or 240 mg/kg in a volume of 8 mL/kg (administration time: 8:00 to 12:00 a.m. JST). The control group was administered WFI in the same manner. Furthermore, 14 days after the initial administration of fucoidan, the cryopreserved virus stock solution was prepared to 5 × 10^3 PFU/mL using DMEM (Dulbecco's Modified Eagle's Medium, Sigma, Saint Louis, MO), and the mice were infected with influenza virus by intranasal instillation of 50 μL. In the first study, body weight, rectal temperature (Model BAT-12, Physitemp Instruments LLC., Clifton, NJ), and pathology scores shown in Table 1 were measured over 10 days postviral infection, and the survival rate (including euthanasia based on humane end points) was recorded. In the subsequent second study, for 3 consecutive days following viral infection, lung tissues were excised after blood collection from the posterior vena cava, and the viral load and various immune indicators were measured.

2.3. Measurement of Viral Load

The excised lungs were minced with pathology scissors, and 2 mL of HBSS was added before homogenizing with a stirrer (NS-51, Microtec Nition, Chiba, Japan). This disrupted solution was filtered through a sterilized mesh (100 μm) to remove cell clumps and impurities, and centrifuged (190g, 5 min) using a centrifuge (AX-310, TOMY DIGITAL BIOLOGY CO., Ltd., Tokyo, Japan); subsequently, about 1 mL of the supernatant was dispensed into serum tubes and cryopreserved (−80 °C). The cryopreserved supernatant was thawed, appropriately diluted with DMEM, and then 0.1 mL of each stock and diluted solution was added to MDCK cells seeded in a 12-well plate to allow the virus to adsorb to the cells for 1 h. A medium containing agarose and neutral red was overlaid, and the number of viral plaques was counted after 3 days of culture.

2.4. Enzyme-Linked Immunosorbent Assay (ELISA)

The collected blood was centrifuged (4 °C, 2200g, 15 min) to recover serum, which was frozen at −80 °C and stored at −30 °C until measurement. After thawing at 4 °C, the antibody and interferon (IFN) concentrations in the serum were measured using the Invitrogen Ig Isotyping Mouse Uncoated ELISA Kit (88−50630, Thermo Fisher Scientific, Carlsbad, CA) and the LEGENDplex Mouse Type 1/2 Interferon Panel (740635, BioLegend Inc., San Diego, CA), respectively.

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2.5. RT-PCR Analysis

The collected lung (left cranial lobe) tissue was immersed in RNAlater Stabilization Solution (AM7020, ThermoFisher) and stored frozen at −30 °C. After thawing the tissue, it was minced with pathology scissors and homogenized in 1 mL of RNAiso PLUS (9109, Takara Bio Inc., Shiga, Japan). Based on the manufacturer's recommendations, total RNA was extracted using chloroform, and washed and recovered by isopropanol and ethanol precipitation. The obtained total RNA was dissolved in DEPC treated-Water (36415−25, Nacalai Tesque INC., Kyoto, Japan), and complementary DNA was synthesized by reverse transcription using the PrimeScript RT reagent Kit (Perfect Real Time) (RR037A, Takara Bio). Using the obtained cDNA as a template, real-time PCR was performed using TB Green Premix Ex *Taq*II (Tli RNaseH Plus) (RR820A, Takara Bio). The primers used for PCR were purchased through the Perfect Real Time support system (Takara Bio), and the target gene expression levels were measured using the Mx3000P Real-Time QPCR System (Agilent Technologies Inc., Santa Clara, CA).

2.6. Statistical Analysis

Pathology scores were analyzed using the Wilcoxon rank-sum test, and survival rates were analyzed using the log-rank test. Other measurement results between two groups were analyzed using One-way ANOVA followed by Tukey's multiple-comparison test. Measured values were expressed as mean ± standard error (n = 5). The significance level was set at 5%, and a difference of less than 5% ($p < 0.05$) and less than 1% ($p < 0.01$) were judged as significant, respectively.

3. RESULTS

3.1. Effects of Oral Administration of *C. okamuranus*-Derived Fucoidan on Influenza Infection Symptoms

Initially, Balb/c mice were administered *C. okamuranus*-derived fucoidan at doses of 30, 80, and 240 mg/kg, and then infected with the H1N1 influenza virus. Over 10 days, conditions during infection (eyelid closure, ruffled fur, decreased activity, respiratory distress, decreased rectal temperature, weight loss) were scored on a 0 to 3 (or 4) scale according to the criteria shown in Table 1. The infection symptoms in this study were most prominent in the order of (B) ruffled fur > (F) body weight > (E) body temperature > (D) respiration > (C) behavior > (A) eyelids, and Figure 1 shows their cumulative values. In the control group and the 30 mg/kg fucoidan-administered group, symptom onset occurred on day 3 postinfection, followed by a rapid deterioration in pathology from day 5 onward. Conversely, in mice administered 80 mg/kg or more of fucoidan, the deterioration of pathology from day 3 to day 5 postinfection was gradual, and the score values were significantly lower on days 6 and 7 compared to the control group. Furthermore, whereas the control group showed no signs of recovery until day 10 postinfection (end of the study), administration of 30 mg/kg or more of fucoidan led to a shift toward remission after day 8.

3.2. Effects of Oral Administration of *C. okamuranus*-Derived Fucoidan on Mouse Survival and Viral Proliferation

Next, states on food intake, rectal temperature, body weight, and survival rate were evaluated during the same study period. As a result, no significant difference was observed in food intake among the groups (Figure 2A), but rectal temperature and body weight tended to show lower values in the control group from day 7 postinfection onward (Figure 2B, C). Additionally, while the survival rate of the control group sharply declined from day 7 onward and was completely

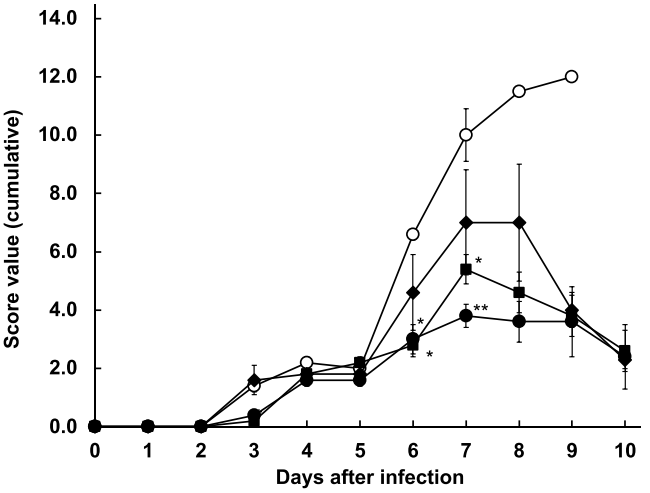


Figure 1. Effects of oral administration of *C. okamuranus*-derived fucoidan on symptom development in flu infection. Balb/c mice administered 30 (rhombus), 80 (closed circle) and 240 mg/kg (square) *C. okamuranus*-derived fucoidan and water (open circle) for 14 days were infected with H1N1 influenza virus, and then, conditions of the flu-infected mice were monitored every 10 days and kept the score. Data were indicated as mean ± SE and were significantly different at $*p < 0.05$ and $**p < 0.01$ (n = 5) in Wilcoxon rank-sum test.

decimated by day 9, the 30 mg/kg fucoidan ingestion group was limited to a 40% decrease in survival rate, and furthermore, all animals survived with the administration of fucoidan at doses of 80 and 240 mg/kg, demonstrating a significant infection-preventive effect (Figure 2D). Based on the above results, the fucoidan dosage was set to 80 mg/kg in the subsequent studies, and the lung viral titer was measured over 3 days postviral infection. As a result, in mice preadministered with 80 mg/kg fucoidan for 14 days, the lung viral titers on days 1, 2, and 3 postinfections were 30%, 42%, and 49% lower, respectively, compared to the control mice, indicating a significant suppressive effect in all instances (Figure 3).

3.3. Systemic Immune Response to Influenza Virus Infection

Subsequently, to evaluate the systemic immune function following viral infection, blood was collected from mice at 1, 2, and 3 days postinfection, and serum concentrations of IFNs and antibodies were measured. Although an increasing trend in IFN-γ concentration (not statistically significant) was observed 1 day postinfection in mice administered *C. okamuranus*-derived fucoidan, no other marked effects were observed for IFN-α, β, or γ (Figure 4). Additionally, no significant impact of fucoidan administration was observed on IgM (acting in the early response), IgG2a (induced by type 1 helper T cells), or any other class of antibodies (Table 2).

3.4. Local Immune Response to Influenza Virus Infection

Finally, to examine the immune response in lung tissues, the primary local sites of viral infection, the gene expression levels of various cytokines and immune cell marker proteins were measured using real-time PCR. Compared to the IFN gene expression dynamics of the control group, in mice administered *C. okamuranus*-derived fucoidan, IFN-α expression continuously increased over 3 days, with significantly higher IFN-α expression observed on day 3 postinfection (Figure 5). Regarding IFN-γ, a robust expression response was noted on

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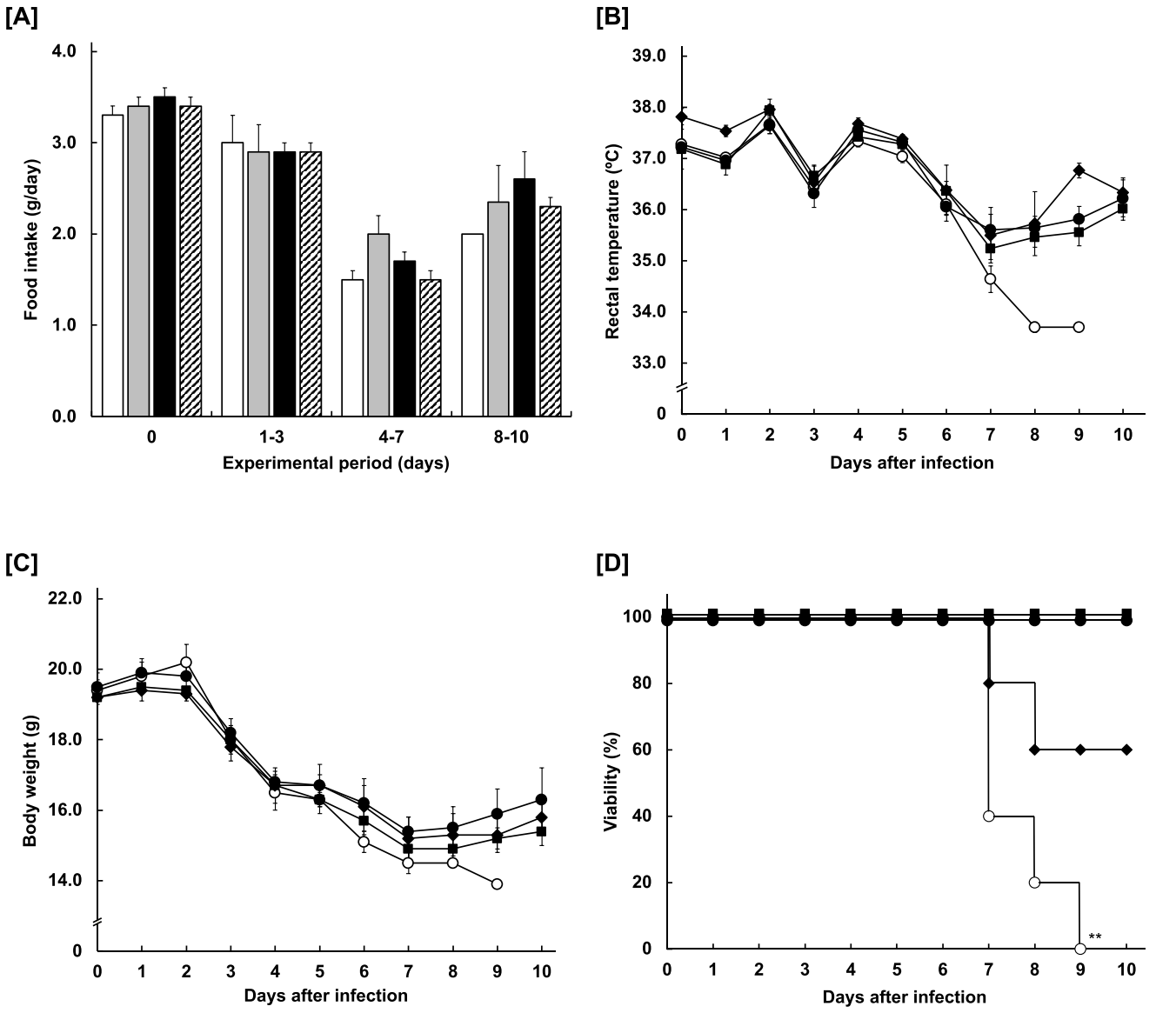


Figure 2. Effects of oral administration of *C. okamuranus*-derived fucoidan on growth of mice infected with lethal dose of flu virus. Balb/c mice administered 30 (gray column or rhombus), 80 (closed column or circle) and 240 mg/kg (hatched column or square) *C. okamuranus*-derived fucoidan and water (open column or circle) for 14 days were infected with H1N1 influenza virus, and then the food intake [A], rectal temperature [B], body weights [C] and viabilities [D] were monitored every 10 days. Data were indicated as mean ± SE. Significant difference at $^{**}p < 0.01$ ($n = 5$) were observed in the viability of fucoidan administered group as compared with control group as a result from log-rank test.

day 2 postinfection; although it decreased slightly on day 3, IFN-γ expression remained higher in the fucoidan-administered group compared to the control group (Figure 5).

Furthermore, the expression level of CD11c, a general dendritic cell marker, rose rapidly from 1 day postinfection and tended to be higher in the fucoidan-administered group over the 3-day period. Similarly, the expression of CD103, a cDC marker, tended to be higher in the fucoidan-administered group on days 2 and 3 postinfection (Figure 6). For Siglec-H, a pDC marker, the expression level increased over time from day 1 to day 2 postinfection, tended to be higher in the fucoidan-administered group than in the control group, and was maintained at a significantly higher level in the fucoidan group on day 3 postinfection (Figure 6).

The accumulation of helper T cells, cytotoxic T cells, and natural killer (NK) cells in the lungs was evaluated via the gene expression of CD4, CD8, and NK1.1 markers, respectively. In all cases, these levels were either trending higher or were significantly elevated in the fucoidan-administered mice (Figure 7). Moreover, the expression levels of the FasL, perforin, and granzyme genes, which are involved in the elimination of virus-infected cells, also trended higher in the fucoidan-administered group compared to the control group (Figure 7).

Lastly, measurements of the gene expression levels of interleukin (IL)-15 and the IL-15 receptor, which are involved in the tissue accumulation of dendritic cells, revealed an induction pattern similar to that of Siglec-H upon viral infection, with higher expression noted in the fucoidan-administered group (Figure 8).

4. DISCUSSION

In this study, significantly lower infection pathology scores and improved survival rates were observed in mice orally

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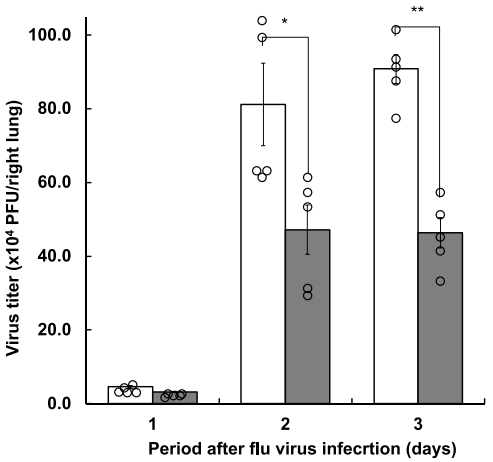


Figure 3. Effect of oral administration of *C. okamuranus*-derived fucoidan on virus expansion in the lung. Balb/c mice administered 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and virus titers were measured for 3 consecutive days. Data were indicated as mean ± SE and were significantly different at $*p < 0.05$ and $**p < 0.01$ ($n = 5$) in Tukey's multiple-comparison test.

administered 80 mg/kg or more of *C. okamuranus*-derived fucoidan starting 14 days prior to H1N1 influenza virus infection. It has been reported that oral administration of fucoidan derived from *U. pinnatifida* is taken up by the Peyer's patches through M cells, thereby inducing the expression of immune regulatory genes.[19] Therefore, it was inferred that *C. okamuranus*-derived fucoidan also activated intestinal immune cells involved in the surveillance of pathogenic foreign substances, and that these cells would spread into the systemic circulation and reach the local site of infection. On the other hand, Trompette *et al.* demonstrated that water-soluble dietary fibers, such as inulin, contributed to the prevention of influenza by activating innate and cellular immune responses, which was achieved by altering the gut microbiota to increase the production of short-chain fatty acids (SCFAs), particularly butyrate.[20] To elucidate the mechanism by which *C. okamuranus*-derived fucoidan prevents influenza infection, further investigations will be necessary not only into the dynamics of fucoidan accompanying antigen uptake but also into its effects on the intestinal environment including the immune-regulating gut microbiota and the production of SCFAs.

Regarding *U. pinnatifida*-derived fucoidan, previous studies have shown that it induces an increase in influenza virus-specific antibody titers in similar mouse infection models, as well as in elderly individuals administered influenza vaccines.[12,21] In contrast, the oral administration of *C. okamuranus*-derived fucoidan to mice infected with the influenza virus in the current study did not affect blood antibody titers across any antibody class. We previously reported that splenocytes from healthy mice treated with *U. pinnatifida*-derived fucoidan produced elevated levels of antibodies.[22] Thus, the modulation of antibody production might be a physiological activity more characteristic of *U. pinnatifida*-derived fucoidan than *C. okamuranus*-derived fucoidan.

Moreover, no significant differences resulting from the administration of *C. okamuranus*-derived fucoidan were observed in blood levels of type I and type II IFNs. This finding is consistent with a previous report demonstrating that while the administration of 6 g/day of *C. okamuranus*-derived fucoidan to human T-cell leukemia virus type 1 (HTLV-1)-infected patients resulted in a significant reduction of peripheral blood viral load, it had no effect on the populations of dendritic cells, NK cells, and T cells in the blood.[23] Consequently, it is presumed that the viral infection-preventive effect of *C. okamuranus*-derived fucoidan is exerted through a mechanism distinct from the enhancement of systemic humoral immunity (antibody production) observed with *U. pinnatifida*-derived fucoidan.

To assess the local replication of the influenza virus and the status of the pulmonary immune system, lung tissues were excised over 3 days postinfection to measure viral loads and IFN expression levels. The results indicated a significant suppression of viral proliferation associated with fucoidan administration as early as day 2 postinfection. Furthermore, IFN-α gene expression continuously increased in the fucoidan-administered group from day 1 and a significant up-regulation

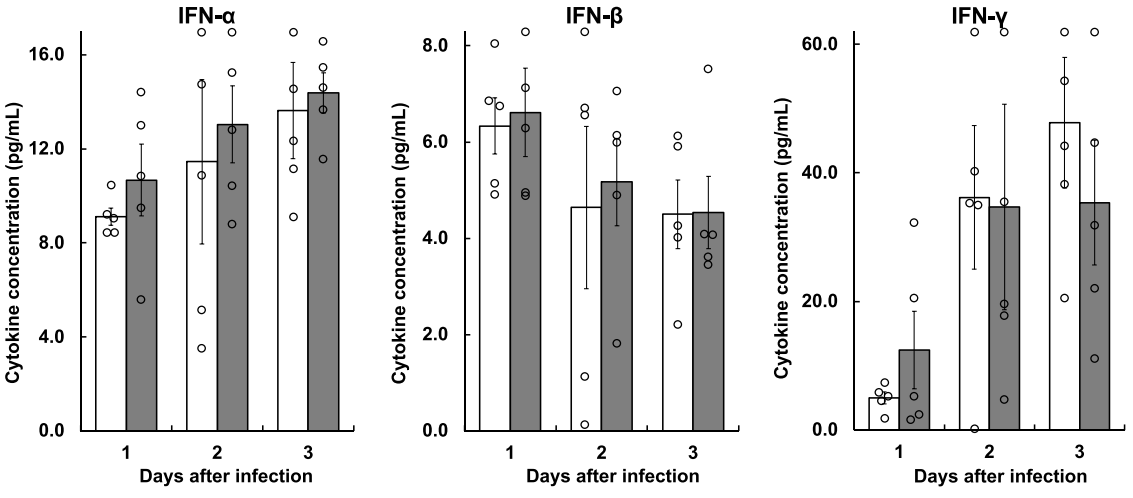


Figure 4. Effect of oral administration of *C. okamuranus*-derived fucoidan on antiviral cytokine contents in sera. Balb/c mice administered 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with influenza virus and cytokine concentration in the caudal vena cava blood were measured for 3 consecutive days. Data were indicated as mean ± SE.

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Table 2. Serum Immunoglobulin Isotype Contents after Oral Administration of *C. okamuranus*-Derived Fucoidan[a]

	IgG1		IgG2a		IgG2b		IgG3	
	Control	Fucoidan	Control	Fucoidan	Control	Fucoidan	Control	Fucoidan
Day 1	475 ± 21	433 ± 20	714 ± 14	699 ± 7	901 ± 5	909 ± 6	122 ± 3	68 ± 4
Day 2	441 ± 12	458 ± 9	703 ± 12	712 ± 5	876 ± 13	897 ± 7	69 ± 4	60 ± 2
Day 3	460 ± 44	375 ± 10	726 ± 25	651 ± 15	930 ± 3	932 ± 6	63 ± 2	53 ± 5
	IgA		IgM		Kappa		lambda	
	Control	Fucoidan	Control	Fucoidan	Control	Fucoidan	Control	Fucoidan
Day 1	247 ± 25	198 ± 14	712 ± 5	702 ± 5	61 ± 1	59 ± 0	334 ± 13	314 ± 5
Day 2	186 ± 25	203 ± 11	686 ± 8	701 ± 4	60 ± 1	59 ± 0	324 ± 3	311 ± 13
Day 3	192 ± 26	163 ± 8	733 ± 6	742 ± 3	62 ± 1	61 ± 1	320 ± 7	316 ± 8

[a]Balb/c mice fed 80 mg/kg of fucoidan derived from C. okamuranus were infected with H1N1 influenza virus, and contents of immunoglobulin isotypes in serum prepared from caudal vena cava blood were measured for 3 consecutive days.

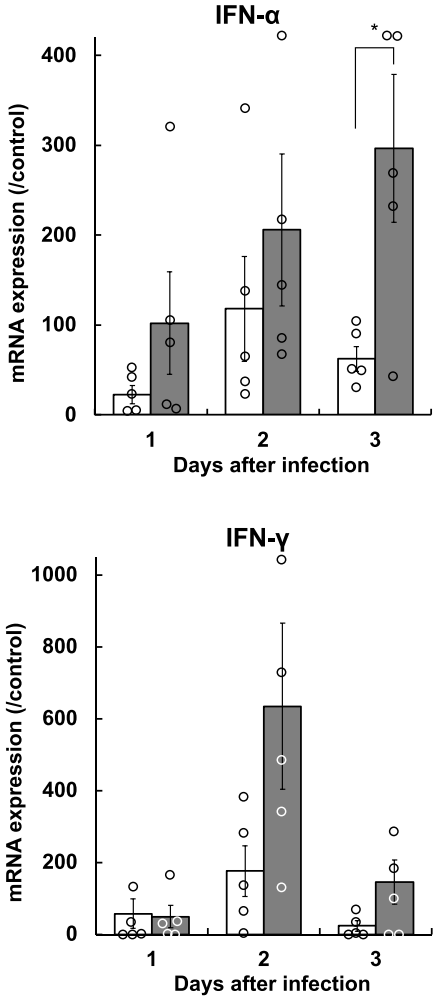


Figure 5. Effect of oral administration of *C. okamuranus*-derived fucoidan on antiviral cytokine expression in the lung. Balb/c mice fed 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and mRNA expressions in the lung were measured for 3 consecutive days. Data were indicated as mean ± SE and were significantly different at $*p < 0.05$ ($n = 5$) in Tukey's multiple-comparison test.

was observed at day 3 postinfection. IFN-α is a critical cytokine predominantly produced by pDCs to induce early antiviral responses.[24,25] The elevated gene expression of Siglec-H, a pDC marker,[26] suggested an increasing trend or significantly enhanced pDC activity in the lungs of fucoidan-administered mice from day 1 postinfection onward. Additionally, it has been reported that fucoidan derived from *Fucus vesiculosus* exhibits similar physiological effects, such as enhancing IFN-α production in response to hepatitis B virus infection and activating transcriptional signaling pathways associated with type I IFN induction in GM-CSF-differentiated mouse bone marrow dendritic cells.[16,27] These findings suggest that the prophylactic administration of *C. okamuranus*-derived fucoidan elicits the immediate recruitment of pDCs to the local infection site (the lung tissue) as an early response to influenza virus infection.

Following the induction of type I IFN expression in pDCs, alveolar macrophages, or epithelial cells, these cells likely augment cellular immune responses via the activation of cDCs.[28−30] Consistent with this, the characteristic genes for CD103 (a cDC marker) and IFN-γ (which enhances cellular immunity) were more strongly expressed in the fucoidan-administered mice from day 2 postinfection onward compared to the control mice.[31] Furthermore, gene expression analysis of immune cell markers suggested enhanced accumulation of CD4-positive T cells (helper T cells), CD8-positive T cells (cytotoxic T lymphocytes, CTLs), and NK cells in fucoidan-administered mice.[32] It is also expected that the expression of FasL and perforin/granzyme, which mediate the elimination of virus-infected host cells, was upregulated. However, in this study, only gene expression levels in the whole lung were measured, so the source of cytokines and the activation status of individual immune cells are still unclear. Therefore, in future experiments, more detailed cellular analyses should be conducted using flow cytometry, including cell identification based on multiple CD markers and the expression of effector proteins containing cytokines and death receptor-related molecules in each cell population.

Previous studies have shown that *C. okamuranus*-derived fucoidan contributes to the activation of the innate immune system, including macrophages and dendritic cells.[10,33] Therefore, we postulate that the cooperative interaction between cDCs and pDCs amplifies immune responses to viral infections through a positive feedback loop within the lung tissue.[17,34] Consequently, these events likely induce the mobilization of Th1 cells, which are crucial for activating antiviral immunity, as well as effector cells such as CTLs and NK cells, to the site of infection.

Unfortunately, the mechanism by which immune cells, particularly dendritic cells activated by fucoidan in the intestinal immune system, reach the local infected site remains unclear. However, this study demonstrated that the oral

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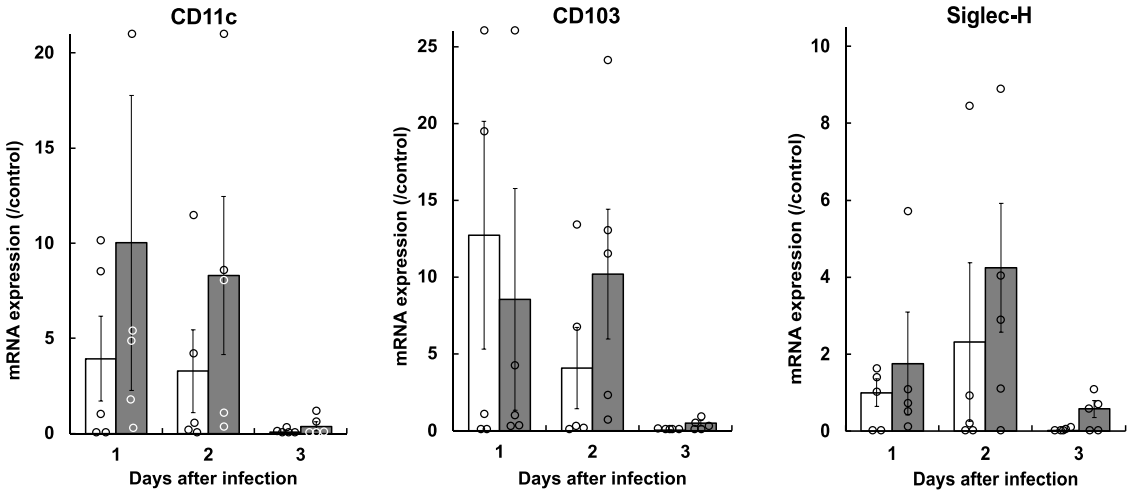


Figure 6. Effect of oral administration of *C. okamuranus*-derived fucoidan on accumulation of dendritic cells (both cDC and pDC) into the lung. Balb/c mice fed 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and expression of marker molecules in the lung were measured for 3 consecutive days. Data were indicated as mean ± SE.

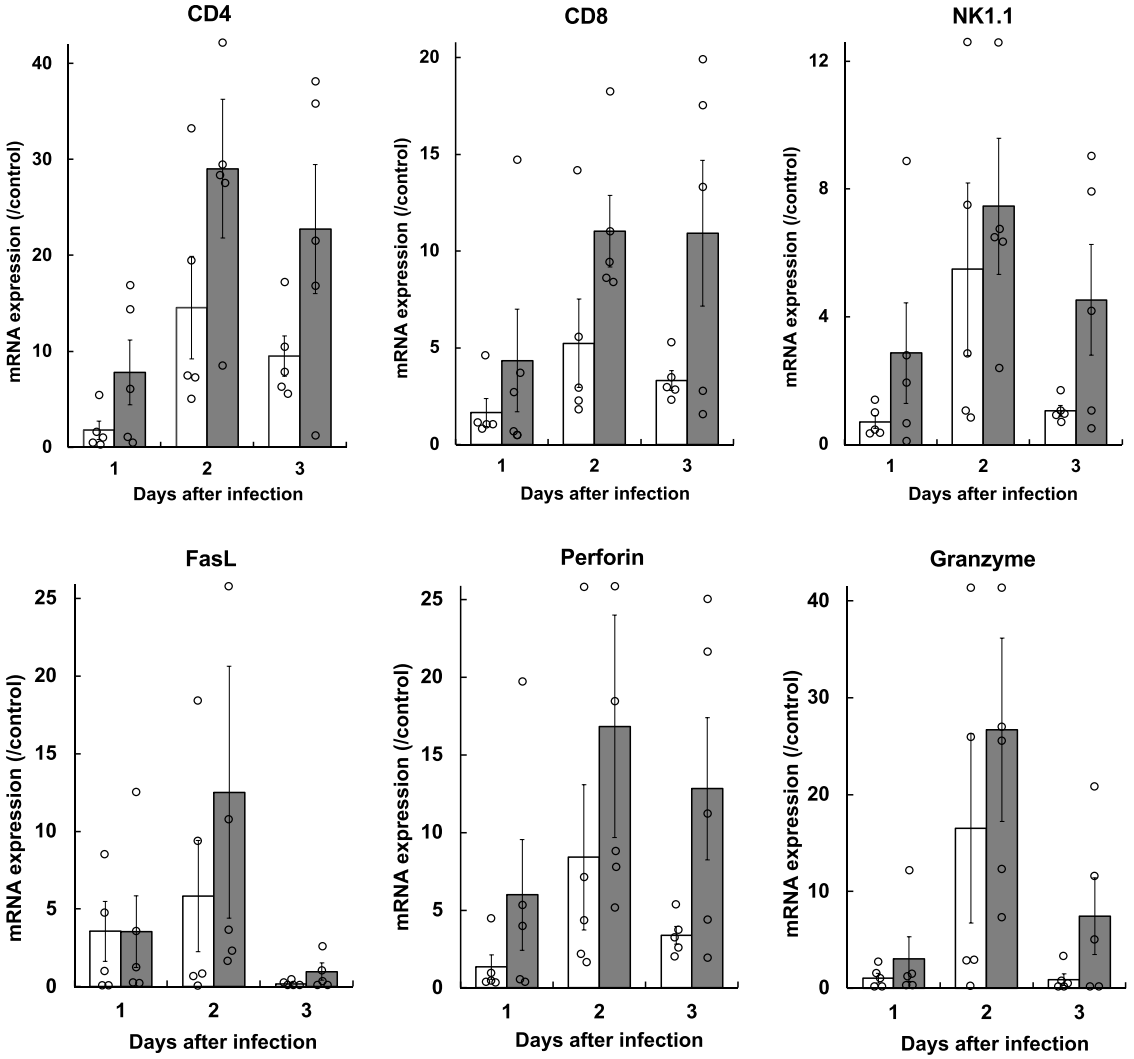


Figure 7. Effect of oral administration of *C. okamuranus*-derived fucoidan on accumulation of lymphocytes (T cells and NK cells) into the lung. Balb/c mice fed 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and expression of marker proteins and cytotoxic molecules in the lung were measured for 3 consecutive days. Data were indicated as mean ± SE.

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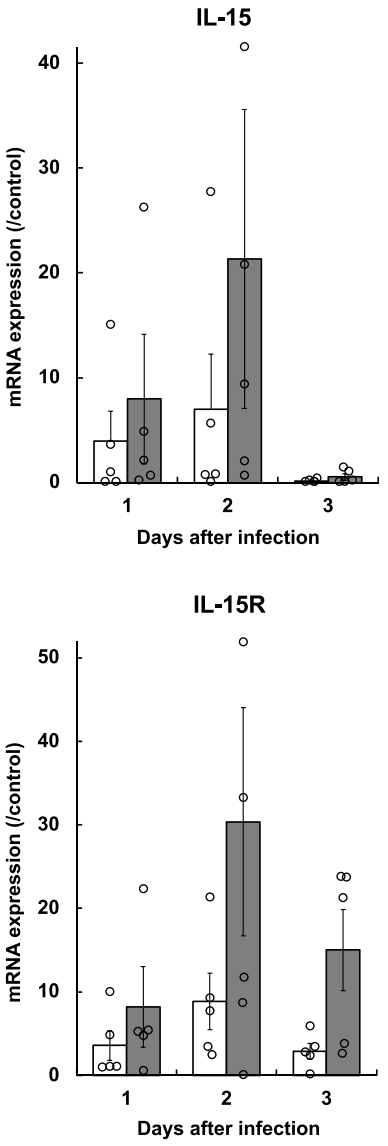


Figure 8. Effect of oral administration of *C. okamuranus*-derived fucoidan on expression of IL-15/IL-15R in the lung. Balb/c mice fed 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and expression of marker molecules in the lung were measured for 3 consecutive days. Data were indicated as mean ± SE.

administration of *C. okamuranus*-derived fucoidan enhanced the pulmonary gene expression of IL-15 (essential for the early accumulation and activation of CTLs and NK cells during influenza infection)[35−37] and IL-15R (which binds IL-15 on dendritic cells and facilitates trans-presentation to effector cells).[38,39] Thus, we hypothesize that dendritic cells, activated by stimuli from orally administered *C. okamuranus*-derived fucoidan, migrate to the pulmonary mucosa where they produce and present IL-15 via IL-15R. This pathway serves as a critical factor in the rapid and potent induction of a protective immune response against influenza virus infection in the upper respiratory tract. As key challenges remaining for future research, further *in vivo* experiments using IL-15/IL-15R neutralizing antibodies or knockout mice will be necessary to validate this hypothesis.

It is frequently observed that pneumonia, accompanied by excessive activation of immune cells, occurs as another clinical phenomenon in influenza virus infection.[40] Therefore, it cannot be ruled out that the activation of immune cells associated with the administration of fucoidan, as observed in this study, potentially progresses to pneumonia. Although the present study did not examine lung tissue histology and therefore could not provide definitive proof, it is inferred that severe pneumonia did not occur based on the alleviation of infection symptoms and the maintenance of survival rates in mice administered fucoidan. Furthermore, gene expression levels in the lungs of G-CSF receptor, neuropeptide Y, and SOCS3,[41−43] which known as inflammatory markers in influenza infection, were measured. The results showed that G-CSFR and neuropeptide Y expression levels were comparable to those in the control group, while SOCS3 expression, although increased by fucoidan administration until 1−2 days postinfection, showed low levels by day 3 postinfection (Supporting Figure 1). SOCS3 is a transcription factor involved in the suppression of the IFN response, and the increase in its expression on days 1−2 postinfection is thought to constitute a feedback response. In addition, we evaluated the mitigating effect of fucoidan on pneumonia in aggravated upper airway infection with a model mouse in which a solution of TLR ligands were injected via oropharyngeal aspiration to simulate lung inflammation. In the previous study, oral administration of 30 mg fucoidan mix formula did not induce inflammation in the intact mice and effectively ameliorated pneumonia in the model mice (nonpublished data).

The human equivalent dose based on body surface area, derived from the murine dosage, is 6.5 mg/kg.[44,45] Therefore, an intake of approximately 300 to 500 mg per day of *C. okamuranus*-derived fucoidan for an adult weighing 50 to 80 kg will be equivalent to the 80 mg/kg dosage in mice evaluated in present study. Based on these findings, human intervention trials with oral administration of fucoidan will be conducted to determine a safe dosage which also includes consideration of the possibility of inducing pneumonia, and to verify its effectiveness in prevention of influenza infection.

In conclusion, this study demonstrates that the oral ingestion of *C. okamuranus*-derived fucoidan prior to viral exposure alleviates infection symptoms and suppresses viral replication in the lungs. This suggests a robust preventive effect against viral infection mediated by the enhancement of the antiviral immune response through dendritic cell activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsnutrsci.6c00043.

Additional experimental results on the gene expression levels of inflammation marker proteins in lungs of the flu virus infected mice (Figure S1); effect of oral administration of *C. okamuranus*-derived fucoidan on inflammation marker proteins in the lung. Balb/c mice fed 0 (open column) or 80 (gray column) mg/kg of fucoidan from *C. okamuranus* were infected with H1N1 influenza virus and mRNA expressions in the lung were measured for 3 consecutive days. Data were indicated as mean ± SE and were significantly different at $*p < 0.05$ ($n = 5$) in Tukey's multiple-comparison test (PDF)

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Author Contributions

Y.M. conducted study design, data organization, gene and ELISA analysis, and manuscript writing. Y.N. was involved in study design, peer review, and funding. S.T. and H.T. were involved in study design and peer review; T.M. provided expert opinion as a food scientist; D.T. provided medical expertise from a physician's perspective.

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Notes

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ABBREVIATIONS

cDCs	conventional dendritic cells
CTLs	cytotoxic T lymphocytes
DMEM	Dulbecco's modified Eagle's medium
ELISA	enzyme-linked immunosorbent assay
IFN	interferon
IL	interleukin
NK cells	natural killer cells
NO	nitric oxide
pDCs	plasmacytoid dendritic cells
TNF-α	tumor necrosis factor-α

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