Executive Summary

Research for safe use of probiotics

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▢ Background

As global sales of probiotic products to the public are on the rise, and probiotic products are being increasingly prescribed by doctors, the probiotics market in Korea is also growing fast. Consequently, around 400 cases of such products' adverse effects and presumed adverse events have been reported in Korea during the past two years. However, there is little information on safe use of probiotics that ordinary citizens or concerned clinical experts could refer to. In addition, there is no licensing and adverse case reporting system or any other government measure in Korea that could effectively manage functional health food products including probiotics. As such, there is a need to find reliable evidence about the safety of probiotics by reviewing major probiotic-related literature and analyzing adverse events. In addition, an expert meeting would be helpful in collating relevant evidence and offering accurate information to concerned clinical experts and the public, thereby enhancing public healthcare and reducing unnecessary medical costs.

▢ Objectives

The overall purpose of this study was to inform the public about safe use of probiotics, by reviewing findings of domestic and foreign research on the

subject and integrating opinions of clinical experts. The specific goals of this study were as follows:

- To provide information on safe use of probiotics
- To provide a ground for advanced institutions focusing on functional health food
- To provide reference data for similar cooperative studies in the future

▢ Methods

Ⅰ. Overview of systematic reviews

By applying the method of overview of systematic reviews (OoRs), this study examined and summarized the results of systematic reviews of domestic and foreign literature about the safety of probiotics. It also utilized the outcomes as objective data for a policy debate forum, an information booklet and promotional videos for the public.

Literature to be reviewed in this study was researched in three major foreign databases (Ovid-Medline, Ovid-Embase, and Cochrane Central) and in five main domestic databases (KoreaMed, KMBASE, KISS, RISS, and KisTi). MeSH terms and natural language related to probiotics were used to search for relevant literature more extensively. During the literature selection/exclusion process, two researchers performed the procedure independently according to predetermined standards, and the same researchers then discussed the outcomes until they came to an agreement.

By employing a common data extraction method, a researcher extracted data from the source literature and another researcher reviewed the extracted data. When the two researchers had different opinions, they invited a third party to discuss the matter and reach an agreement.

For risk of bias assessment on the selected sources, the Assessment of Multiple Systematic Reviews (AMSTAR), a tool to assess risk of bias in a

systematic literature review, was adopted. Two researchers carried out an independent risk of bias assessment and then checked whether they produced the same results. When they failed to reach a consensus, they discussed the matter with a third party and the three of them determined the final assessment results based on consensus.

II. Analysis of adverse events

1. Presumed adverse effects reported to the Ministry of Food and Drug Safety

In cooperation with the Ministry of Food and Drug Safety, this study examined all the data on presumed adverse effects reported to the "Functional Health Food Presumed Adverse Effect Reporting System," a program the ministry has been running for the last two years (2014-2015) as part of its integrated civil complaints service. Each year's data were analyzed after classification based on who reported the cases, whether the products were imported, product names, symptoms, disease history, and treatment history. Details of liver and kidney symptoms, cranial nerves and psychiatric symptoms, cardiovascular and respiratory symptoms, and metabolic disorders were reproduced from the original case reports.

2. Analysis of raw data on drug adverse effect reports

Based on the Korea Adverse Event Reporting System(KAERS)'s raw data on probiotic adverse event reports (obtained from the Korea Institute of Drug Safety & Risk Management), each type of adverse event was analyzed using basic statistics and frequency analysis. Causal relationships between adverse effects and causes were shown based on reported cases. Because detailed data on drug adverse effect report cases were not available, this study examined the frequency of probiotic-related adverse effects.

3. Cases reported to the Korea Consumer Agency

Basic statistics and frequency analysis were performed on adverse event

cases reported during three years to the Consumer Injury Surveillance System (CISS), provided by the Korea Consumer Agency.

Ⅲ. Expert meeting

Since a review by clinical experts on the results of the systematic literature review and analysis of adverse events was deemed necessary, we decided to convene an expert meeting. The systematic literature review and analysis of adverse events indicated that adverse events were mostly symptoms and diseases related to the gastrointestinal system. Therefore, an official letter was sent on August 10, 2016 to the Korean Society of Gastroenterology to ask for recommendations of clinical experts who would participate in the meeting. The Korean Society of Gastroenterology recommended four clinical experts, and based on their availability, an expert meeting was held on Friday, August 19, 2016 in a medium conference hall at the National Evidence-based Healthcare Collaborating Agency.

Ⅳ. Policy debate forum

To hold a policy debate forum on the safety of functional health food with Assemblywoman Kim Soon Rye of the Saenuri Party, we visited her office on Monday, June 27 and Tuesday, August, 2016, to explain the outline and results of this study. We also discussed the location and date of the forum, presentation topics, debate agendas, and candidate presenters and panelists.

The forum was held on September 20, 2016, to look for ways to systematically manage functional health food products under the theme of “[Urgent diagnosis] Safety of Functional Health Food, Reality Check”. Key attendees included four presenters from the National Evidence-based Healthcare Collaborating Agency, the Korean Society of Gastroenterology, and the National Cancer Center; four panelists from the Seoul National University Medical College, the Consumer Korea, and the Ministry of Food

and Drug Safety; and a chair from the NECA.

The four-hour long forum consisted of presentations in the first part and a debate and Q&A session in the second part.

▢ Results

Ⅰ. Overview of systematic reviews

1. Results of literature search and selection/exclusion

Based on searches of domestic and foreign literature databases, 162 out of 5,208 systematic literature review papers were ultimately selected for this study. Among the selected literature, this study was focused on 125 research papers that included detailed information regarding safety.

2. Results of risk of bias assessment

By utilizing the AMSTA, risk of bias assessment was conducted on the final 125 selected research papers containing detailed information on safety. The assessors were required to choose one of the four available options- "Yes," "No," "Cannot answer," and "Not applicable" - on 11 items for each paper. It was found that 81 or 64.8% of the 125 papers received a "Yes" response for 8 or more of the 11 items.

3. Analysis of selected literature

Based on the disorders or symptoms the subjects were suffering from, the research results were sorted into seven categories: 1) general population, 2) preterm and/or low birth weight infants, 3) gastrointestinal system, 4) skin and allergic diseases, 5) urinary and genital diseases, 6) respiratory diseases, and 7) others, and each of the seven categories was divided again into sub-groups to describe the final results, presented below.

① General population: Neonatal necrotizing enterocolitis and neonatal mortality were identified as serious adverse events, yet a statistically

significant risk difference was not observed between the probiotic and control groups, or the probiotic group showed a significantly lower risk. Other adverse events were gastrointestinal disorders, infection and infestation, vomiting, flatulence, abdominal discomfort, diarrhea, and atopic dermatitis, none of which showed a significant intergroup difference or the probiotic group turned out to have a lower risk.

② Preterm and/or low birth weight infants: Neonatal necrotizing enterocolitis, sepsis, mortality, and hospitalization duration were reported as severe adverse events, and other adverse events included vomiting and enteral feeding. In terms of both severe and other adverse events, the probiotic and control groups did not have a statistically significant risk difference or the probiotic group showed a significantly lower risk.

③ Gastrointestinal system: Neonatal necrotizing enterocolitis, myoclonic jerks, hospitalization duration, all-cause mortality, infections or emergency room visits, infection of necrotic pancreatic tissue, abdominal abscess requiring surgery, systemic inflammatory response syndrome, and organ failure were reported as serious adverse events, yet the probiotic and control groups did not show a statistically significant risk difference or the probiotic group recorded a significantly lower risk. Other adverse events included stomachache, headache, chest pain, abdominal bloating, vomiting, skin rash, diarrhea, nausea, meteorism, local complications, and other infections, but the intergroup risk difference was not statistically significant. Literature on short bowel syndrome patients, however, found that the probiotic group showed adverse events of sepsis and D-Lactic acidosis, indicating a need for further research.

④ Skin and allergic diseases: Although sepsis developed by a patient who took probiotics was reported as a serious adverse event, it was not from the ultimately selected literature, but from a case report. In terms of other adverse events, diarrhea, vomiting, and flatulence were reported, but there was no statistically significant intergroup risk difference.

⑤ Urinary and genital diseases: Headache, increased appetite, pruritus,

diarrhea, nausea, vomiting, and vaginal symptoms were reported as other adverse events, and the probiotic group had a statistically significant lower risk.

⑥ Respiratory diseases: Vomiting, diarrhea, enteralgia, flatulence, and nausea were reported as other adverse events, but the risk difference between the probiotic and control groups was not statistically significant.

⑦ Others(cancer patients, ICU patients, surgical patients, patients consuming antibiotics, patients suffering a complex disease and others): The severe adverse events reported were all-cause mortality, ICU and in-hospital mortality, ICU-acquired infection, ICU-acquired and ventilator-associated pneumonia, ICU catheter-related bloodstream infection, length of ICU stay, and post-operative septic complications, but there was no statistically significant risk difference between the probiotic group and the control group. Other adverse events included appendicitis, nausea, vomiting, heightened blood pressure, diarrhea, abdominal cramps, and abdominal bloating; yet the two groups did not show a statistically significant difference in risk or the probiotic group showed a lower risk. On the contrary, literature on patients consuming antibiotics indicated that use of probiotics by preterm infants and patients with a suppressed immune system (including organ transplant patients) could lead to fungemia, liver infection, endocarditis, hepatic abscess, and bacteremia, and indicated central venous catheter contamination and others as major causes. According to papers on patients suffering from a complex disease, sepsis, meningitis, and infection of other organs were mostly observed among patients who took Lactobacillus. Moreover, some sepsis cases were found among newborn babies and patients who underwent central venous catheterization.

II. Results of adverse event analysis

1. Analysis of presumed adverse effects reported to the Ministry of Food and

Drug Safety

Although 355 cases of presumed adverse effects of probiotics were reported in 2014, the figure went down to 40 in 2015. The cases were examined according to who reported them, whether the products were imported, symptoms, and disease and treatment history. It was found that consumers reported 366 cases, accounting for the largest share of reporters. There were 280 cases of gastrointestinal symptoms, 26 cases reported by subjects who had a pre-existing disease and 63 cases where subjects who received treatment. There were seven presumed cases, out of 395, of probiotics' adverse effects on liver and kidney in the entire two-year data (2014-15).

2. Analysis of adverse drug effect reports

Considering probiotic-related adverse drug effects reported each year, 39 cases (26.0%) were reported in 2013, while 23 cases (15.3%) were reported in 2014. For the decade from 2006 to 2015, reports on 150 adverse drug reaction cases were made. In terms of body organs, clinical cases among the probiotic-related reports of adverse effects can be sorted into: symptoms of gastrointestinal system disorders including 46 cases (30.7%) of diarrhea, 13 cases (8.7%) of gastrointestinal distress, and 11 cases (7.3%) of vomiting; 21 cases (14.0%) of skin disorder symptoms such as skin rash and urticaria; and other various symptoms. Among those reports, one case (0.7%) of hospitalization or extension of hospitalization duration and another case (0.7%) of other medically serious situations were clinically significant adverse events. It was estimated that consuming probiotics in conjunction with other drugs could possibly cause a severe adverse reaction.

3. Analysis of cases reported to Korea Consumer Agency

Adverse events related to probiotics that consumers reported consisted of 43 cases(34.7%) filed in 2013, 45 cases(36.3%) in 2014, and 36(29.0%) in 2015. The majority of the 124 cases submitted to the Consumer Injury Surveillance System(CISS) were 38 cases(53.7%) of specific adverse events due to food consumption or physical symptoms of organ damage and pain in the digestive system and 11 cases(16.4%) of urticaria, apart from cases of diarrhea and skin symptoms.

Ⅲ. Expert meeting

Clinical experts from the Korean Society of Gastroenterology thought it was appropriate that the results of the systematic literature review had been grouped into seven categories(general population, preterm and/or low birth weight infants, gastrointestinal system, skin and allergic diseases, urinary and genital diseases, respiratory diseases, others) before being examined. However, they did not provide specific opinions on the results of the adverse event analysis. Some opined that proper regulations and public educational programs are necessary, given some cases overseas where adverse events were triggered by certain strains, lack of procedure that tests purity of strains contained in functional health food products, and indiscriminate use of a variety of strains whose benefits and effectiveness are unproven.

Ⅳ. Policy debate forum

1. Issues regarding functional health food (from the perspective of consumers)

According to the results of Consumer Korea's 2015 survey, major issues regarding functional health food were: ① false and exaggerated advertisements about effects, ② lack of objective evidence on effects, and ③ lack of information on product safety as well as on distribution of products that failed safety certification.

2. Safety of probiotics(from the perspective of medical experts)

The review of research papers on probiotic safety confirmed that adverse effects of probiotics are limited to some high-risk patients, and it is believed that medical experts are paying enough attention to this risk group. As such, it appears that the public need not be too concerned about the safety of probiotics.

3. Functional health food safety management systems currently in place (from the perspective of concerned agencies)

The Ministry of Food and Drug Safety examines the scientific basis of safety and effectiveness of every functional health food product before it is launched in the market, and has made it mandatory for precautions to be printed on all product packaging. Moreover, the ministry keeps track of safety and effectiveness of functional health food products that are already available in the market, and continues monitoring false/exaggerated advertisements and adverse effect cases.

4. Transfer of functional health food certification authority (from the perspective of concerned agencies)

Transferring the authority of certifying functional health food products from the government to a private organization is deemed untimely. Japan is implementing a system that combines government certification and private certification; however, Korean consumers still maintain strong faith in the Ministry of Food and Drug Safety.

5. Suggestions

As participants in clinical trials tend to be healthier than the general public, further observational research should be conducted on various groups of people such as those who are relatively less healthy and those who have possibly been exposed to products available in the market. Such research,

however, requires considerable time and expenditure, and therefore there is a need for a system where people can voluntarily report and keep an eye on adverse events to functional health food (medical experts, researchers, etc.).

Functional health food should be regulated as food, not as drugs, and the system for functional health food should be focused on ① implementing a stricter process of certifying functional health food's benefits and effects, ② tightening the control of ingredients and quality, and ③ strengthening the monitoring on false/exaggerated advertisements and providing certified information (medical experts, consumer representatives).

The Ministry of Food and Drug Safety is currently conducting a safety review on functional health food products before they reach the market, yet a reappraisal must be performed after the products become available in the market (medical experts).

Adverse events from functional health food should be systematically controlled and there is a need for guidelines on safe consumption of such products. Furthermore, those products must be accurately labeled to provide information on how to consume them (medical experts, consumer representatives, researchers).

▢ Conclusions and policy suggestions

Probiotic products, with their claims about various benefits and positive effects, are being sold in large numbers, and the global probiotics market is expanding at a rapid pace. At the same time, however, cases of adverse events related to probiotics are increasingly being reported. In regards to this issue, this study conducted an overview of systematic reviews and an analysis of adverse reaction cases to examine whether probiotics are safe, and it found the following:

- When people in normal health consumed probiotics, they suffered from stomachache, diarrhea, abdominal bloating, or other mild adverse events, but most of them were temporary events.
- Patients suffering from various disorders including atopic dermatitis, acute infectious diarrhea, and H. pylori infection did not exhibit statistically significant minor or severe adverse events to probiotics.
- However, as some patients with a suppressed immune system or preterm infants have shown adverse events like sepsis and bacteremia, patients who fall into these risk groups should consult a professional doctor or get a prescription before consuming probiotics.

In addition, based on the aforementioned findings, we would like to make the following suggestions:

1. Probiotic products have been classified as both functional health food and drugs so far; however, different licensing standards are applied to drugs and functional health food products, and reports of adverse event cases are being collected by the National Food Safety Information Service under the Ministry of Food and Drug Safety, the Korea Consumer Agency and the Korea Institute of Drug Safety & Risk Management using different methods and systems. Therefore, a unified review system for licensing as well as a specified, streamlined, and specialized reporting and classification system should be adopted.

2. If those with a weakened or a suppressed immune system, such as cancer patients or preterm infants, consume probiotics, they could experience an adverse reaction. Thus, implementing a precautionary labeling system, distributing an information booklet for the public, or other measures should be adopted so that Korean citizens can consume probiotics more safely.

3. Although people are given abundant clinical information on probiotic safety and effectiveness, no system monitors and analyzes such information. Therefore, a monitoring and research support system should be established, using which experts such as medical professionals from the concerned academic organizations can voluntarily collect, analyze, and disseminate information on adverse events from a neutral stance.

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Key words

probiotics, safety, adverse effects, adverse event, harm