

An Irregular Movement

Challenges of Commercialising Pre and Postbiotics in Asia Pacific

Future of Microbiome 2022
Nyx Chong

KYOWA
HAKKO
BIO



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Improving lives with health science

A proud member of:



**HMOs.
The Formula
for Success.**


Human Milk Oligosaccharides

 **KYOWA** | 2023



**Unique.
Patented.
Postbiotic.**

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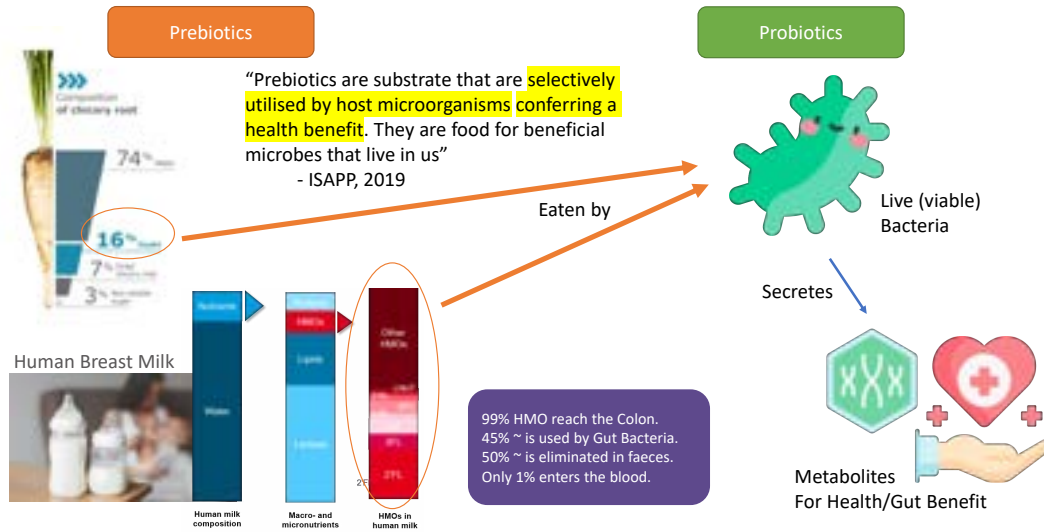
**HMOs.
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Definitions of Biotics



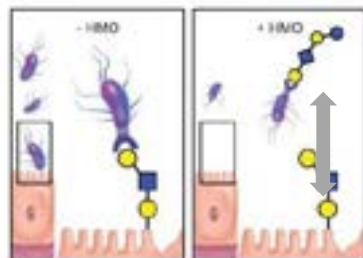
HMO Elimination: A Unique Immune Advantage



Mechanism of antipathogenic function of HMO

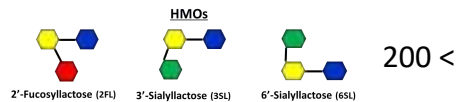
1. Inhibition of Pathogen Attachment (Decoy Effect): Attributes to HMO structures

Structural Similarity of HMOs to receptors on cell surface allows inhibition of pathogen attachment



Bode L. Glycobiology. 22(9):1147-62, 2012

Structural Diversity of HMOs leads to versatile antipathogenic function



Virus

- Influenza virus
- Norovirus
- Rotavirus
- Respiratory syncytial virus



Bacteria

- Group B streptococcus (GBS)
- Campylobacter jejuni
- Helicobacter pylori
- Pseudomonas aeruginosa

HMO: Reduces rate of Diarrhea in Children



Observational study

Infants and toddlers consuming breast milk with high 2FL content have significantly less cases of diarrhea of *Campylobacter jejuni*



| Pathogen (bacteria/virus) | HMOs | Anti-infective mode of action | Notes |
|-----------------------------|-------|---|---|
| <i>Campylobacter jejuni</i> | 2'-FL | Invasion protection, inhibition of adhesion | Organisms causing food poisoning. Major causative agent of campylobacteriosis |

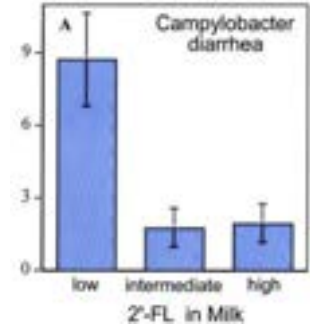
Diarrheal illness in children caused by contaminated food

In December 2015, the World Health Organization (WHO) issued estimates of human disease damage attributable to food. As a statistical value in 2010...

- ✓ 600 million patients and 420000 deaths worldwide due to exposure to contaminated food
- ✓ 4.6 billion patients with diarrhea and 1.6 million deaths from diarrhea worldwide.
- ✓ 548 million patients with diarrhea caused by pathogens. Of these, 217 million patients were children < 5 years old.

Perspectives: Diarrhoeal disease in children due to contaminated food
Bulletin of the World Health Organization 2017;95:233-234

Number of Diarrhea cases
(Studied in 93 mother-infant pairs for 2 years)



HMO: Promotes Bifidobacterium Colonisation



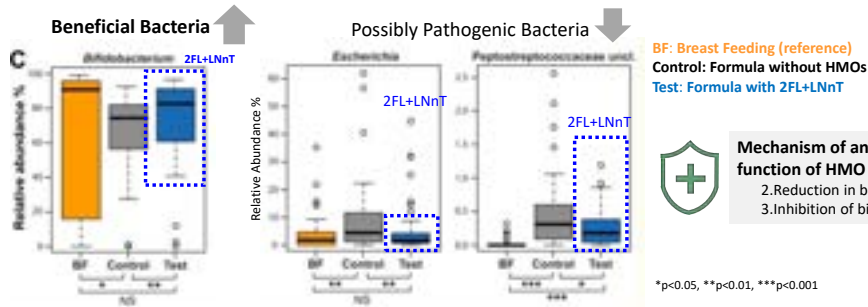
Clinical Trial

2FL and LNnT supplementation to infant formula helped growth and colonization of beneficial bacteria in infants.

[Subject] Healthy infants (0-14 days after birth, 146)

- Breast feeding group: Mother-infant reference group (BF group)
- Standard IF (Control group).
- 2FL: 1.0-1.2g/L+LNnT:0.5-0.6g/L combined (Test Group)

[Method] Administration from enrollment (0-14 days) to 6 months



HMO: Changes microbiota in IBS Adults



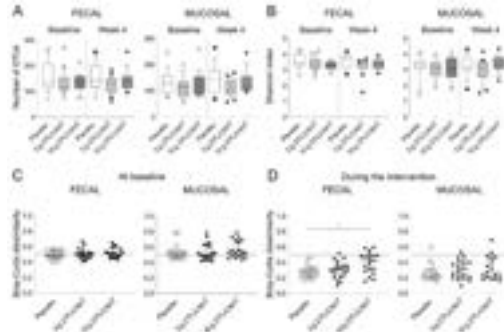
Interventional study

2FL and LNnT supplementation to Irritable Bowel Syndrome Patients resulted in change of microbiota, fecal and plasma metabolites in 4 weeks.

[Subject] Irritable Bowel Syndrome Patients (n=58) were given one treatment for 4 weeks

- 5g of 4:1 mix of 2'FL/LNnT
- 10g of 4:1 mix of 2'FL/LNnT
- No supplement given (Control group)

[Method] Fecal and mucosal microbial composition measured at baseline and after intervention



Iribarren C. *Nutrients*. 13(11):3836, 2021

HMO Function: Brain Development



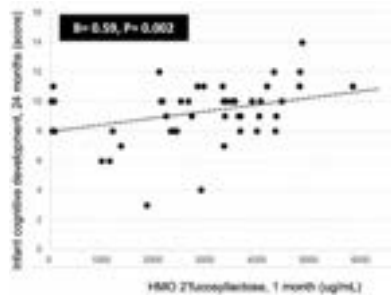
Observational study

Positive correlation between concentration of 2FL and cognitive development, and 3SL and language development.

There was a positive association between the amount of **2FL** contained in breast milk at 1 month of age and higher cognitive growth at 24 months of age ($\beta = 0.59$, $p=0.002$)

3SL content in breast milk was positively correlated with language development in A-tetra+ group*.

(*Alpha-Tetrasaccharide, A-tetra is an HMO only present in milk from blood type A women)



Berger PK et al., *PLoS One*. 12;15(2):e0228323, 2020.

| | | 2'-FL | 3'-SL | 6'-SL |
|---|-----------------|--------|-------|-------|
| ELC score (Early Learning Score) | Estimate | -0.001 | 13.12 | 0.038 |
| | <i>p</i> value | 0.189 | 0.002 | 0.635 |
| Receptive language (receptive language) | Estimate | -0.47 | 9.95 | 0.022 |
| | <i>p</i> value* | 1 | 0.015 | 1 |
| Expressive language (Display language) | Estimate | -0.258 | 7.53 | 0.053 |
| | <i>p</i> value* | 1 | 0.048 | 1 |

*: Adjusted *p* value

Cho S. *Am J Clin Nutr*. nqab103, 2021

Recap: HMO Health Benefits



IMMUNE BENEFITS

1. Inhibition of Pathogen Attachment (Decoy Effect/ Adhesion Inhibition)
2. Reduction in bad bacterial growth
3. Inhibition of biofilm formation
4. Immunomodulation (proven in infants; pending adult studies)



GUT BENEFITS

1. Colonisation by Bifidobacteria and other good bacterial growth
2. Reduction in risk of Campylobacter induced diarrhea
3. May prevent dysbiosis related to disease conditions or age



COGNITIVE BENEFITS

1. Association with language and cognitive development for children
(more data needed for effects in elderly)

Challenges in expanding HMO use



Limited use for HMOs allowed due to lack of studies in non-infants/ non-child population

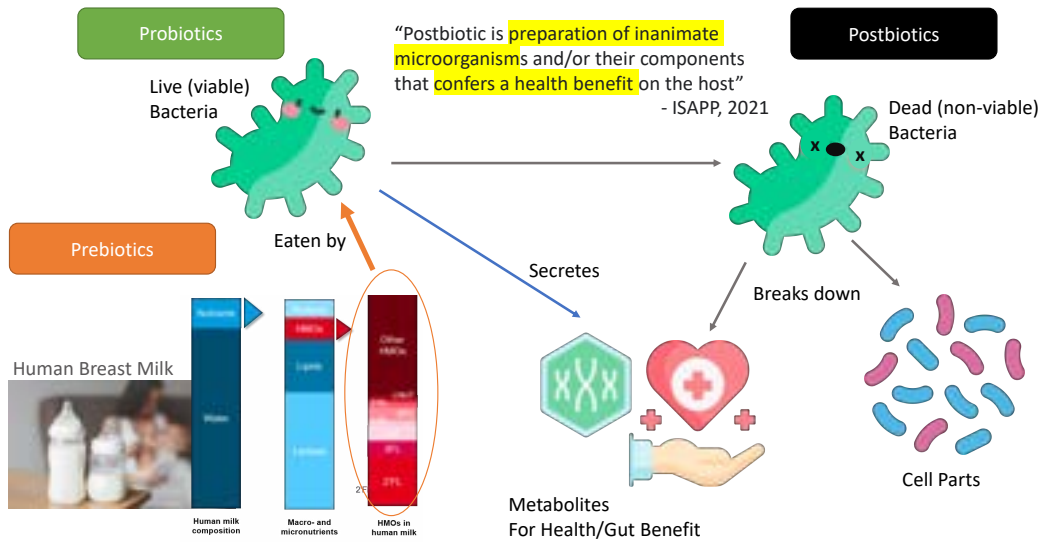
How can we expand application of ingredients through including other demographics?

Rate of HMO adoption is slow due to (1) Lack of Awareness and (2) Cost of ingredients in Southeast Asia

How can we make HMOs more accessible?



Definitions of Biotics KYOWA



Postbiotic Definition



COMPONENTS OF A POSTBIOTIC:

- Postbiotics may contain heat-killed bacteria, microbial cells
- and/or microbial cell fragments/metabolites...
- with or without metabolites/bioactive products

POSTBIOTIC:

- Derived from microorganisms, but a postbiotic does not have to be derived from a probiotic
- A deliberate process to remove cell viability, metabolic byproducts, and/or other components
- Yields cells or elements or metabolites that are stable
- Evidence of a health benefit in the target host
- Assessment of safety of the postbiotic preparation for the intended use

THE POSTBIOTIC DEFINITION EXPLAINED:

Postbiotics is derived from "biotic" relating to being organisms and "post" meaning after. The preparation is a specific preparation, including microorganisms, metabolites, and bioactive products, which are not the live organisms.

Postbiotics recognizes that the same "heat" or "inactivation" may suggest an array of metabolic, physiological or other capabilities of conferring a health benefit.

Components or ingredients that confer health benefits may be included by a variety of different cell surface molecules.

ISAPP
International Scientific Association for Probiotics and Prebiotics

For more information visit ISAPPscience.org or follow us on Twitter @ISAPPscience

NOT POSTBIOTIC:

- Viruses, including bacteriophages
- Vaccines
- Fillers without cell components
- Purified microbial components (e.g. proteins, peptides, immunomodulators)
- Purified microbial metabolites (e.g. organic acids)

Stammert, et al. Nat Rev Gastroenterol Hepatol (2022) <https://doi.org/10.1038/s41571-021-03660-8>

IMMUSE™



Heat-killed *Lactococcus Lactis* strain Plasma (LC-plasma)

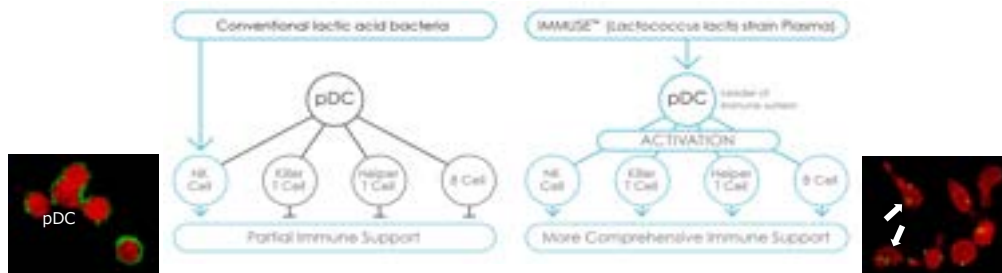
WINNER
NUTRA
INGREDIENTS ASIA
AWARDS 2022



IMMUSE™

Patented | GRAS | Vegetarian | Allergen Free | Clinically Studied | Non-GMO

- Heat-killed *Lactococcus Lactis* strain Plasma (LC-plasma)
- Mechanism of Action: Activation of Plasmacytoid dendritic cells (pDCs)



In over 15 clinical trials, with participants ranging from 6 to 60 years of age, people who consume IMMUSE tend to experience less symptoms of fatigue and illness.

PLoS One, 2012

Health benefit of IMMUSE (Children)

IMMUSE™

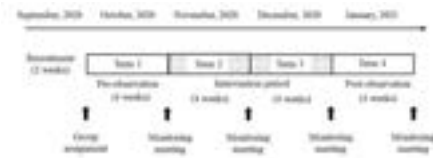
Study design

Result

Subjects: 892 Elementary school children in Vietnam (age of 6-9)

Intervention: 50 mg IMMUSE for 8 weeks

Outcome: Cold like symptoms



| Symptom | Term | Group | Cumulative Days | | p-Value | Odds Ratio (95% CI) |
|------------|--------|-----------|-----------------|----------|---------|---------------------|
| | | | Negative | Positive | | |
| Fever | Term 2 | Control | 12,660 | 108 ** | 0.001 | 0.56 (0.42-0.79) |
| | | LC-Plasma | 12,148 | 60 | | |
| | Term 3 | Control | 12,728 | 40 | 0.93 | 1.02 (0.66-1.58) |
| | | LC-Plasma | 12,169 | 39 | | |
| Cough | Term 2 | Control | 10,340 | 2428 | 0.05 | 1.01 (0.95-1.07) |
| | | LC-Plasma | 9675 | 2333 | | |
| | Term 3 | Control | 10,796 | 2572 | 0.22 | 1.04 (0.98-1.11) |
| | | LC-Plasma | 9675 | 2535 | | |
| Runny nose | Term 2 | Control | 10,811 | 1957 * | 0.07 | 0.94 (0.87-1.01) |
| | | LC-Plasma | 10,437 | 1771 | | |
| | Term 3 | Control | 10,688 | 2080 | 0.83 | 1.01 (0.94-1.08) |
| | | LC-Plasma | 10,207 | 2001 | | |

Nutrients, 2022

Cumulative days of symptoms were significantly decreased

Health benefit of IMMUSE (Adults)

IMMUSE™

Study design

Result

Subjects: 397 healthy adults

Intervention: 50 mg/d IMMUSE for 12 weeks

Outcome: Severity of cold like symptoms

Table 3 - Cumulative number of incident days of each symptom and its severity grade during the intake period.

| Symptoms | | Slight | Mild | Moderate | Severe | p-Value ^a |
|--------------------|---------|--------|------|----------|--------|----------------------|
| Sore throat (n) | Placebo | 375 | 431 | 149 | 71 | 0.076 |
| | IMMUSE | 333 | 344 | 141 | 57 | |
| Sore throat (n) | Placebo | 401 | 154 | 51 | 31 | 0.001 |
| | IMMUSE | 416 | 118 | 31 | 17 | |
| Cough (n) | Placebo | 441 | 312 | 61 | 21 | 0.001 |
| | IMMUSE | 346 | 177 | 34 | 6 | |
| Laziness (n) | Placebo | 275 | 117 | 34 | 29 | 0.180 |
| | IMMUSE | 309 | 143 | 32 | 18 | |
| Articular pain (n) | Placebo | 33 | 29 | 14 | 8 | 0.947 |
| | IMMUSE | 37 | 25 | 30 | 3 | |
| Muscle pain (n) | Placebo | 144 | 71 | 38 | 17 | 0.002 |
| | IMMUSE | 138 | 74 | 31 | 12 | |
| Cold (n) | Placebo | 81 | 35 | 4 | 9 | 0.948 |
| | IMMUSE | 114 | 35 | 12 | 4 | |

^a The cumulative number of incident days of each symptom is listed.
^b For each symptom, the percentages of reduction with each severity grade were compared between the placebo and IMMUSE groups by chi-square test.

J. Func. Food, 2016

Scores of cough and sore throat was significantly reduced

Existing Product ranges



Challenges for IMMUSE

IMMUSE™

Lack of Regulatory understanding of "Postbiotic"

How can we involve regulators in discussion on latest science?

Lack of standardisation for postbiotic products (milligrams? CFUs?)

How can we encourage healthy competition and collaboration for this emerging market?

To Summarise



- Scientists and manufacturers have founded and created exciting new products with promising health benefits.
- It is important to continue to build **inclusive clinical studies** (for all ages, ethnicities, etc.) in order to encourage **new applications for novel ingredients**.
- Just as important as creating new science, is **raising awareness on and involving regulators, consumers, and industry partners** in the advancements of the 'Biotics' landscape.
- Without multi-stakeholder relationships and buy-in, novel ingredients may only remain a pipedream on the benches of a lab.



Thank You!



Discover our Products



KYOWA HAKKO BIO USA
<https://www.kyowa-usa.com/>

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