



Postbiotics: The Newest "Biotic"

The webinar will begin shortly





Postbiotics: The Newest "Biotic"

Mary Ellen Sanders, PhD March 5, 2025

Webinar Housekeeping

- You are muted
- Write questions in the Q&A box
- Postbiotics: The Newest "Biotic" awards 1.0 CPEUs in accordance with the Commission on Dietetic Registration's CPEU Prior Approval Program
 - Assessment, CPE certificate, & slides will be emailed after the webinar

New England Dairy Continuing Education



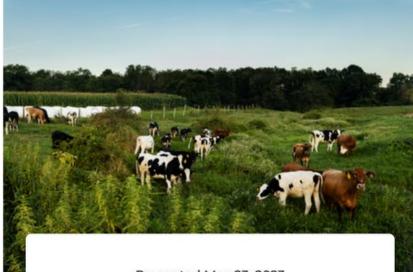
Presented October 25, 2023

Culturally Inclusive, Lactose Intolerant-Friendly Recipes and Cook-Along

Approved for 1.0 hour of CPE by the Commission on Dietetic Registration

Presented by: Tessa Nguyen, MEd, RD

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Presented May 23, 2023

Rethinking Methane: Animal Agriculture's Path to Climate Neutrality

Approved for 1.0 hour of CPE by the Commission on Dietetic Registration.

Presented by: Frank Mitloehner, Ph.D.

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Presented May 10, 2023

Lactose Intolerance Considerations Across Diverse Populations

Approved for 1.0 hour of CPE by the Commission on Dietetic Registration.

Presented by: Constance Brown-Riggs, MSEd, RDN, CDCES, CDN & Tessa Nguyen, MEd, RD

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Webinar Speaker



Mary Ellen Sanders, PhD

Postbiotics: the Newest 'Biotic'

MARY ELLEN SANDERS, PH.D.

MARY ELLEN SANDERS LLC PROBIOTIC CONSULTING

MES@MESANDERS.COM

MARCH 5, 2025 NEW ENGLAND DAIRY WEBINAR

Disclosures over last 2 years

- ISAPP 2023 executive science officer
- Danone NA advisory board
- Pepsico consulting
- Sanofi speaking fee

Learning objectives

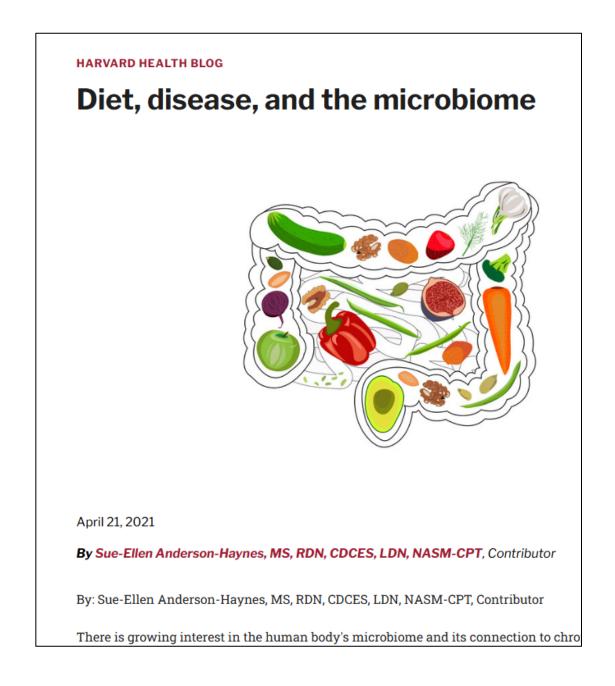
- Define postbiotics and contrast with probiotics, prebiotics, and synbiotics
- Why we might expect dead microbes to have a health benefit
- Understand how fermented foods might deliver postbiotics

The microbiome and its role in health is all the rage

Healthline

How Does Your Gut Microbiome Impact Your Overall Health? The bacteria and other microbes in your gut help you digest food and may support immune, heart, and brain health, among other benefits. Your body is full of trillions of bacteria, viruses and fungi. They are collectively known as the microbiome. While some bacteria are associated with disease, others are actually extremely important for your immune system, heart, weight and many other aspects of health. This article serves as a guide to the gut microbiome and explains why it's so important for your health.

Harvard Health Blog



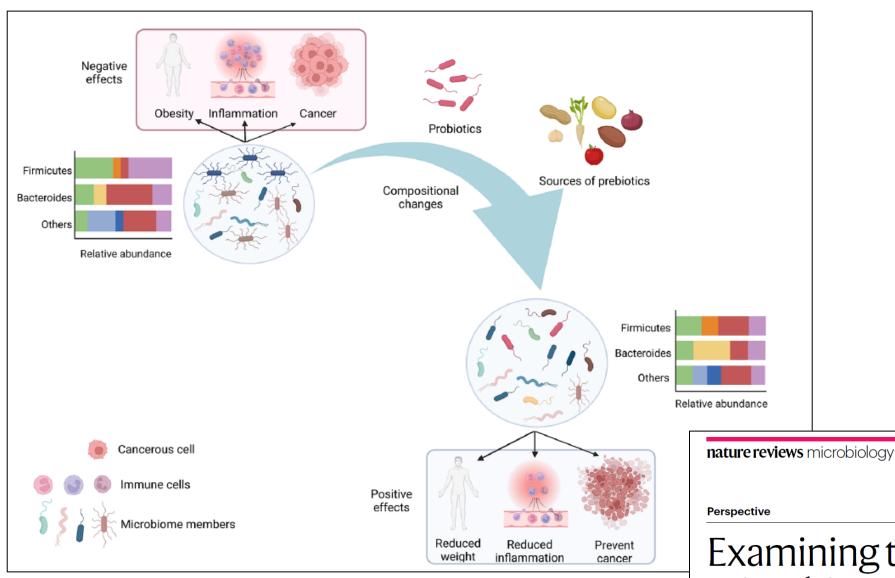
Cleveland Clinic



The big question is – can we modify the microbiome and improve health?

Can we modify the microbiome and improve health?

Conventional thinking:



But...do we know that the microbiota CAUSES these conditions?

Do we know how to change the composition of the microbiota to reverse progression of these conditions?

https://doi.org/10.1038/s41579-024-01107

https://doi.org/10.1021/acs.chemrev.2c00431 *Chem. Rev.* 2023, 123, 31–72; Aggarwal, et al 2023

Examining the healthy human microbiome concept

Raphaela Joos © 12, Katy Boucher © 1, Aonghus Lavelle 13, Manimozhiyan Arumugam © 4, Martin J. Blaser © 5, Marcus J. Claesson 12, Gerard Clarke © 16, Paul D. Cotter © 17, Luisa De Sordi © 8, Maria G. Dominguez-Bello © 9, Bas E. Dutilh © 1031, Stanislav D. Ehrlich 123, Tarini Shankar Ghosh © 14, Colin Hill © 12, Christophe Junot © 15, Leo Lahti © 16, Trevor D. Lawley © 17, Tine R. Licht © 18, Emmanuelle Maguin © 19, Thulani P. Makhalanyane © 20, Julian R. Marchesi © 21, Jelle Matthijnssens © 22, Jeroen Raes © 22,23, Jacques Ravel © 24,25, Anne Salonen 26, Pauline D. Scanlan © 12, Andrey Shkoporov © 12, Catherine Stanton © 17, Ines Thiele 127, Igor Tolstoy 28, Jens Walter © 12,29, Bo Yang © 30,31, Natalia Yutin 28, Alexandra Zhernakova 32, Hub Zwart © 33, Human Microbiome Action Consortium*, Joël Doré © 12,19 & R. Paul Ross © 12

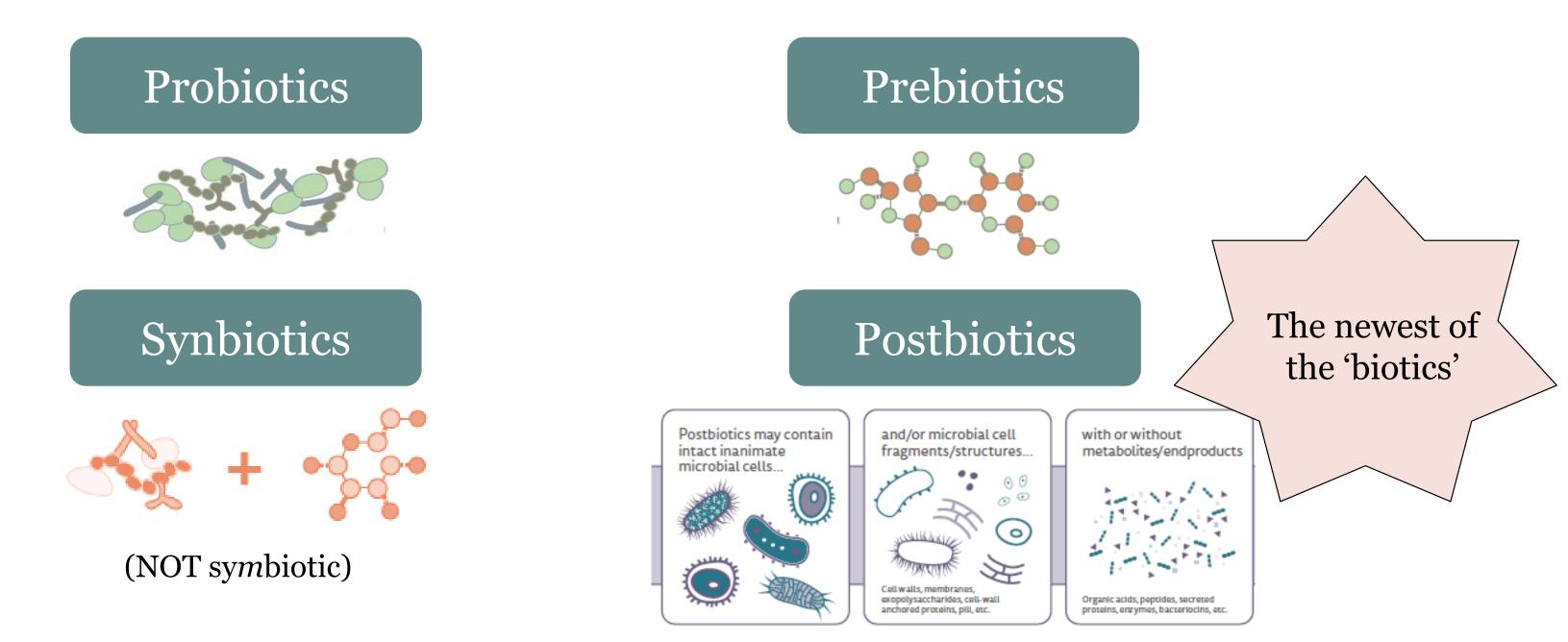
"One of the most controversial issues in microbiome research is the definition of a 'healthy' human microbiome. This concept is complicated by the microbial variability over different spatial and temporal scales along with the challenge of applying a unified definition to the spectrum of healthy microbiome configurations."

https://doi.org/10.1038/s41579-024-01107-0

Diet – including biotics - is one tool to impact the microbiome

The challenge is to focus on the health endpoint, rather than the microbiota-mediated mechanism

'Biotics' family of substances



ISAPP Definitions

Simple conceptualization

Probiotic	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host Hill et al., 2014	Live microbes that confer a health benefit
Prebiotic	A substrate that is selectively utilized by host microorganisms conferring a health benefit on the host <u>Gibson et al., 2017</u>	Food for microbes residing in the host that confers a health benefit
Synbiotic	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host Swanson et al., 2020	A mixture of one or more probiotics plus prebiotics that confers a health benefit
Postbiotic	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host <u>Salminen et al., 2021</u>	Non-viable microbes or microbial fragments with or without metabolites that confer a health benefit

Definitions broad enough to support innovation Do not restrict:

Host (not just humans), regulatory category (not just foods), site of action (not just gut), mechanisms of action (not just microbiota modulation)

Safety for intended use implied for all definitions

Postbiotics





The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics

Seppo Salminen ¹ [□], Maria Carmen Collado², Akihito Endo ³, Colin Hill ^{4,5}, Sarah Lebeer⁶, Eamonn M. M. Quigley ⁷, Mary Ellen Sanders ⁸, Raanan Shamir^{9,10}, Jonathan R. Swann^{11,12}, Hania Szajewska ¹³ and Gabriel Vinderola ¹⁴

130,000 article accesses to date

https://www.nature.com/articles/s41575-021-00440-6

670,000 article accesses for all four "Biotics" papers combines





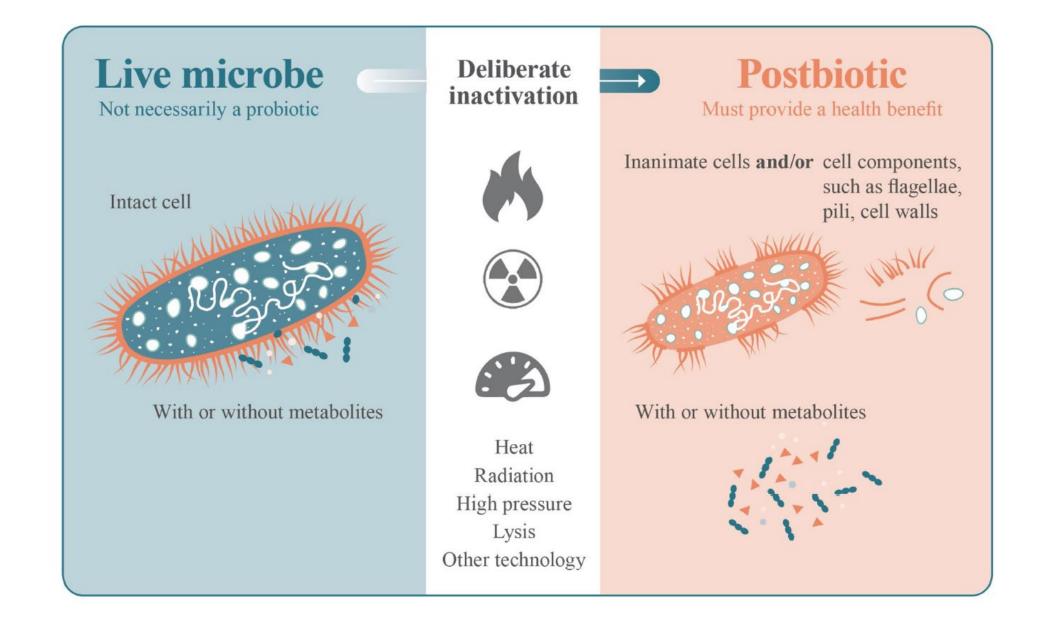
Frequently asked questions about the ISAPP postbiotic definition

Gabriel Vinderola^{1*}, Mary Ellen Sanders², Marla Cunningham³ and Colin Hill⁴



Frontiers in Microbiology

TYPE Perspective
PUBLISHED 10 January 2024
DOI 10.3389/fmicb.2023.1324565



Focus of postbiotics is on dead microbes and microbial cellular components
Metabolites - vitamins, SCFA, antibiotics, etc - <u>not required</u> but may be active
components of a postbiotic
Purified metabolites are not 'postbiotics'

- Confirmed health benefit
 - Label claims must match clinical trials endpoints, study populations, etc

- Derived from well-characterized microbes
 - Defined to the strain level
 - Known genomic sequence

- Well-defined parameters for preparation
 - Changes in preparation could change biological activity of postbiotic

Safe for the intended use

Postbiotics are not...

- X Viruses, including bacteriophages
- ★ Vaccines
- Filtrates without cell components
- Purified microbial components (e.g., proteins, peptides, exopolysaccharides)
- Purified microbial metabolites (e.g., organic acids)

Some have disagreed with the ISAPP definition...



Postbiotics — when simplification fails to clarify

José Eleazar Aguilar-Toalá, Stefania Arioli, Pradip Behare,
Clara Belzer, Roberto Berni Canani, Jean-Marc Chatel, Enza D'Auria,
Mônica Queiroz de Freitas, Eran Elinav, Erick Almeida Esmerino,
Hugo S. García, Adriano Gomes da Cruz, Aarón F. González-Córdova,
Simone Guglielmetti, Jonas de Toledo Guimarães,
Adrián Hernández-Mendoza, Philippe Langella, Andrea M. Liceaga,
Marciane Magnani, Rebeca Martin, Mohammad Tamrin Mohamad Lal,
Diego Mora, Mehran Moradi, Lorenzo Morelli, Fabio Mosca,
Filomena Nazzaro, Tatiana Colombo Pimentel, Chao Ran,
Chaminda Senaka Ranadheera, Maria Rescigno, Azucena Salas,
Anderson S. Sant'Ana, Katia Sivieri, Harry Sokol, Valentina Taverniti,
Belinda Vallejo-Cordoba, Jaroslav Zelenka, and Zhigang Zhou

Reply to: Postbiotics — when simplification fails to clarify

Seppo Salminen, Maria Carmen Collado, Akihito Endo, Colin Hill, Sarah Lebeer, Eamonn M. M. Quigley, Mary Ellen Sanders, Raanan Shamir, Jonathan R. Swann, Hania Szajewska, and Gabriel Vinderola

Key objection to the ISAPP definition:

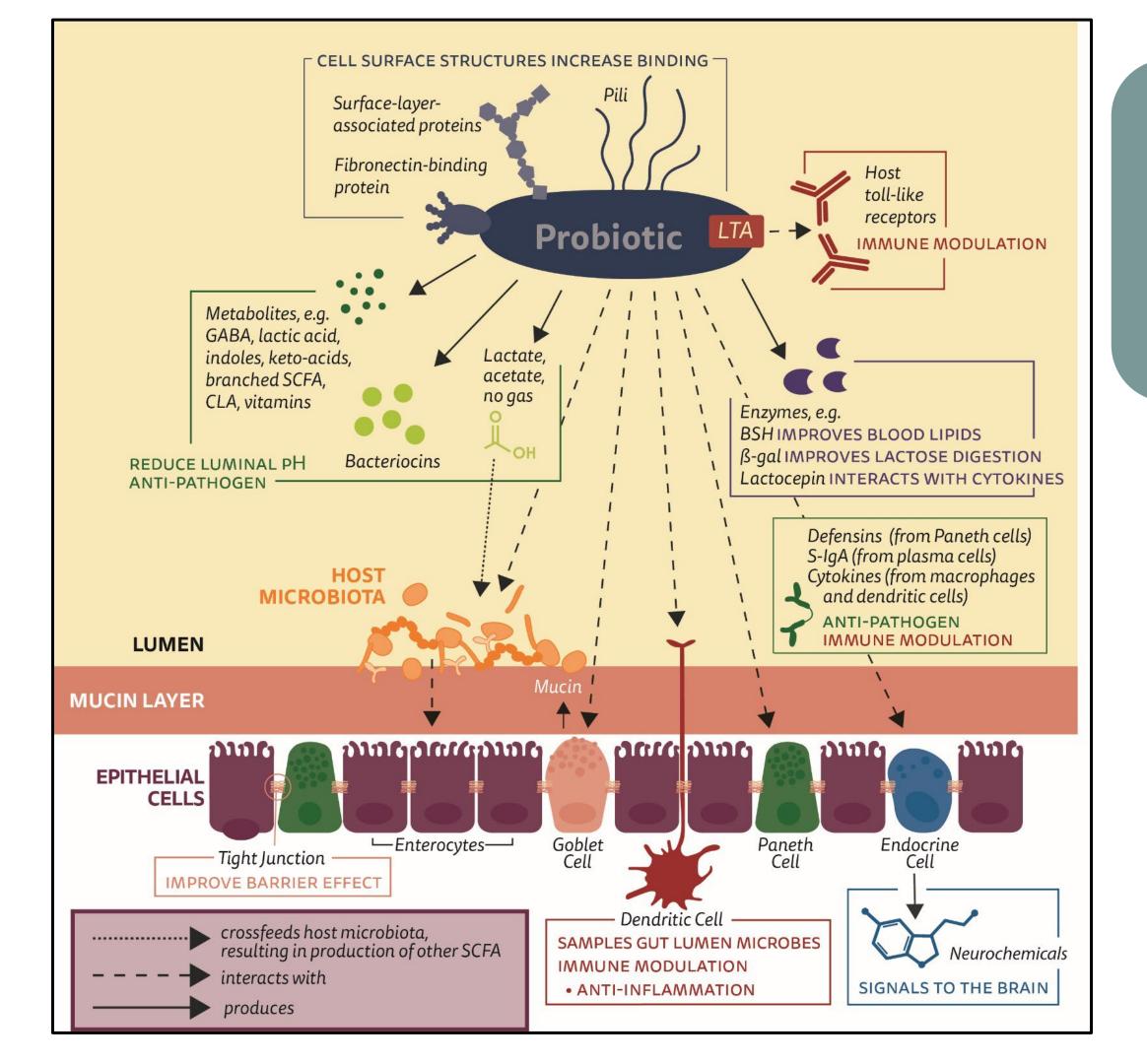
Metabolites vs dead cells

Postbiotic: Post (after) biotic (life) (Not 'from life')

This is an emerging field - now is the time to develop consensus around a definition

Advantages to postbiotics

- Perceived safety compared to probiotics: absence or very small number of live microbes opportunistic infections, transfer of antibiotic resistance genes
- Stability: don't need to keep microbes alive through storage
- Cold chain may not be needed: increased geographical distribution options



Mechanisms for postbiotics more limited than for probiotics

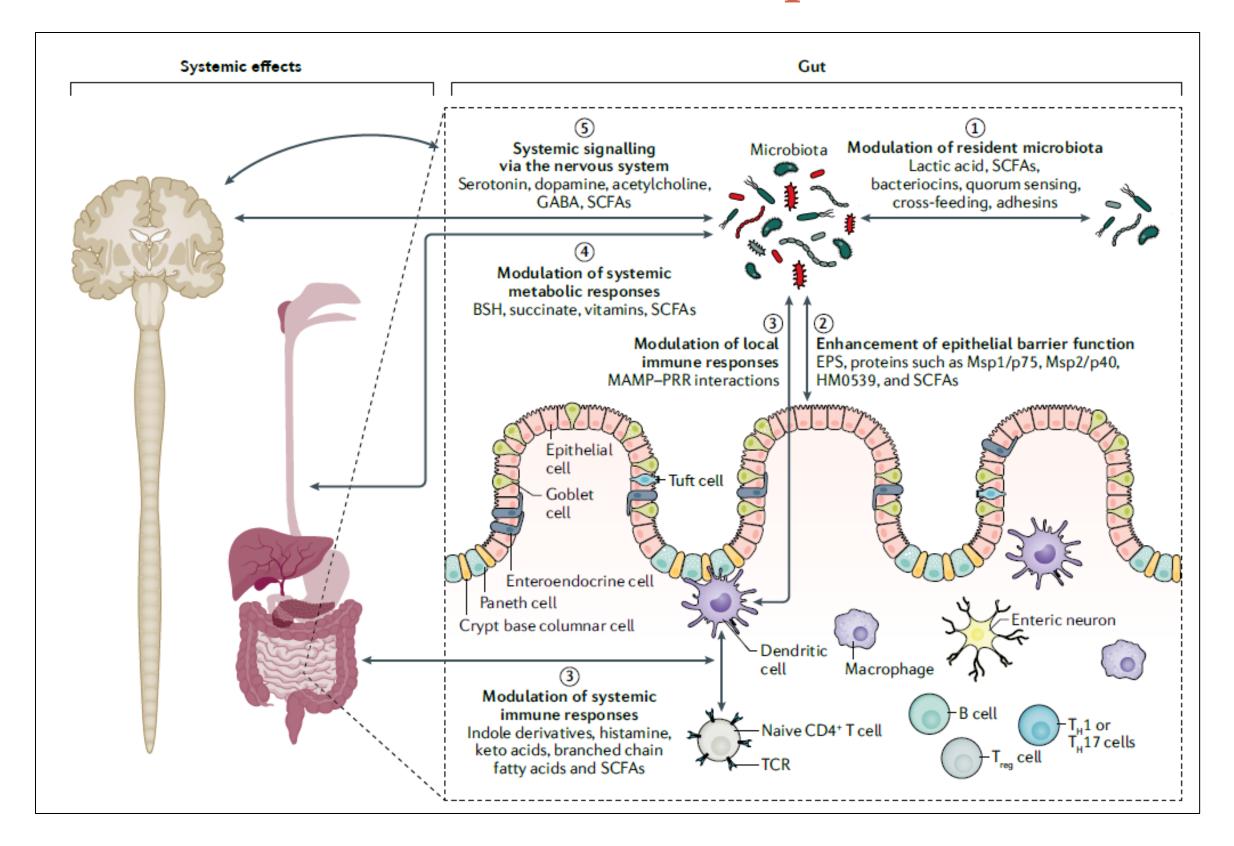
Figure from:

Evidence-based use of probiotics, prebiotics and fermented foods for digestive health

March 2021, Today's Dietitian

http://viewer.zmags.com/ publication/c85ca1bd#/c 85ca1bd/1

Postulated mechanisms of postbiotics



https://www.nature.com/articles/s41575-021-00440-6
Fig 4, Salminen et al. 2021

Same strain – live or dead

AP&T Alimentary Pharmacology and Therapeutics

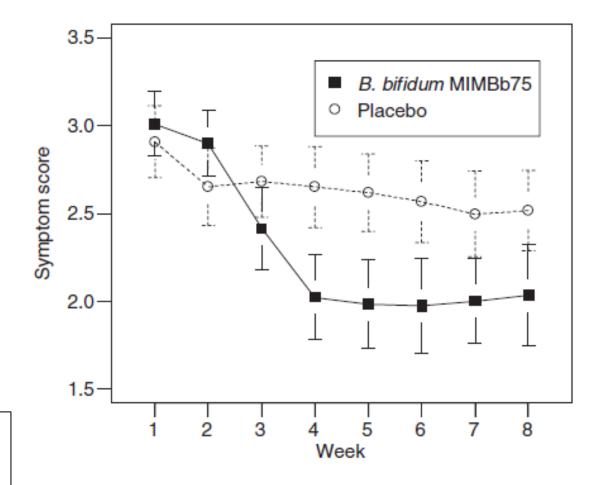
Randomised clinical trial: *Bifidobacterium bifidum* MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life — a double-blind, placebo-controlled study

S. Guglielmetti*, D. Mora*, M. Gschwender* & K. Popp*

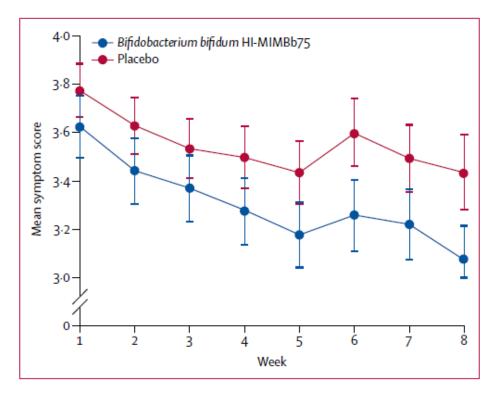
Heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial

Viola Andresen, Jürgen Gschossmann, Peter Layer

At the end of treatment, significantly improved compared with placebo: health-related quality of life, IBS symptom scores, and global symptom relief.



	Bifidobacterium bifidum HI-MIMBb75	Placebo	p value*
IBS-SSS	-101	-71	0.0013
IBS-SSS (PP)	-102	-74	0.0048
Bowel movement satisfaction†	-23.7	-16-6	0.021
Days with pain†	-22.7	-14·3	0.0080
Impact on daily life†	-20.1	-14-2	0.012
SGA of IBS symptoms	-0.76	-0.54	0.013
Abdominal pain‡	-1.29	-0.93	0.011
Distension or bloating§	-0.69	-0.50	0.046
Composite score 1–4	-1.21	-0.89	0.026
Discomfort§	-1.35	-0.92	0.0015
Pain associated with bowel movement§	-0.88	-0.46	0.023
SF-12 sum score	5.82	4.06	0.038
SF-12 mental health sum score	3.31	1.66	0.031
SF-12 physical health sum score	2.51	2.40	0.90
Number of bowel movements per week (in constipation-predominant subgroup)	1.7	-1.0	0.022

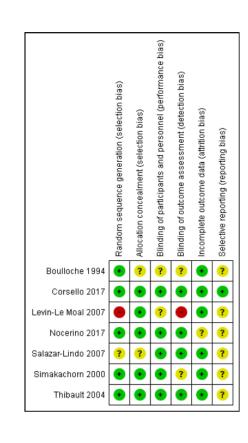


Postbiotics in infant nutrition

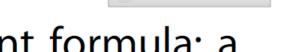


- Systematic review through March 2019 of RCTs
- Children <5 years
- Prevent or treat CIDs
- 7 RCTs/1740 children met inclusion criteria (not many studies)
- Heat-killed *L. acidophilus* LB \downarrow duration of acute diarrhea (\downarrow 20 hrs)
- Heat-killed *L. paracasei* CBA L74 \downarrow risk diarrhea (RR 0.51), pharyngitis (RR 0.31), laryngitis (RR 0.44)

"There is limited evidence to recommend the use of specific postbiotics for treating pediatric diarrhea and preventing common infectious diseases among children."



SYSTEMATIC REVIEW



Check for updates

Safety and efficacy of adding postbiotics in infant formula: a systematic review and meta-analysis

Xifeng Liang^{1,2}, Yu Li^{1,2}, Zhijiao Zhao¹, Ru Ding¹, Jing Sun^{3,4™} and Cheng Chi p^{2™}

Pediatric Research (2024) 95:43–51; https://doi.org/10.1038/s41390-023-02813-w

- 9 RCTs, 2065 subjects
- No impact on SAEs, daily weight gain, total gain in body length and daily head circumference gain
- No impact on infantile colic, flatulence, diarrhea, vomiting, abdominal pain and gastrointestinal disorders

"Our study provides evidence that the addition of postbiotics to infant formula is safe but not effective."



Table 1. Characteristics of 9 included randomized controlled trials.

	Country	Year		Intervention met	thods	Sample size	Age at baseline
First Author			Interven tion time	experimental group	control group	(Intervention/contr ol)	
Béghin, L.	France, Germany, Italy	2021	6 months	fermented infant formula	nfant formula	140(70/70)	7 d
Campeott o, F.	Australia	2011	Until the hospital	Fermented preterm formula and breast milk	Preterm formula and breast milk	58(24/34)	3 d
Huet, F.	Belgium, France, Ireland	2016	up to 17 weeks of age	Fermented formula with prebiotics	Nonfermented formula with prebiotics	154(79/75)	≤28d
Rodriguez -Herrera, A.	Italy, Spain	2019	up to 17 weeks of age	Fermented formula with scGOS/lcFOS	Nonfermented nfant formula without scGOS/lcFOS	199(94/105)	≤28d
Roggero, P.	Italy	2020	3 months	Fermented formula	Standard infant formula	52(26/26)	≤7d
Thibault, H.	France	2004	5 months	Fermented infant formula and breast milk	Standard infant formula and breast milk	913(464/449)	4-6m
Vandenpla s, Y.	Belgium, Hungary, Poland, Spain, Ukraine	2020	up to 17 weeks of age	Fermented formula with postbiotics	Infant formula with scGOS/lcFOS	196(101/95)	≤14d
Vandenpla s, Y.	Belgium, Ireland, France	2017	up to 17 weeks of age	Fermented formula with scGOS/IcFOS	Infant formula with scGOS/lcFOS	213(109/104)	≤28d
Plaza- Diaz, J.	Spain	2022	12 months	Standard formula with postbiotics and breast	Standard formula and breast milk	140(70/70)	21d

Lack of harmony in what is defined as a 'postbiotic intervention':

Fermented formula

Prebiotics

Postbiotics – but how defined?

SYSTEMATIC REVIEW

Safety and efficacy of adding postbiotics in infant formula: a systematic review and meta-analysis

Check for updates

Xifeng Liang^{1,2}, Yu Li^{1,2}, Zhijiao Zhao¹, Ru Ding¹, Jing Sun^{3,4 \boxtimes} and Cheng Chi \bigcirc ^{2 \boxtimes}

Pasteurized Akkermansia muciniphila



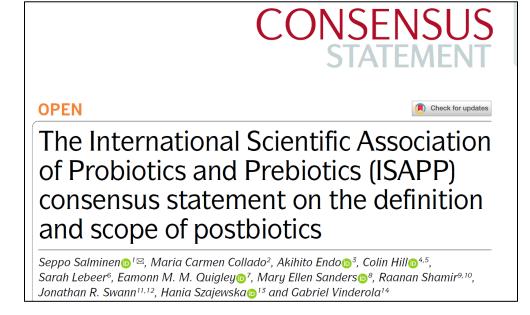
Compared to placebo:

- Improved insulin sensitivity (+28.62 \pm 7.02%, *P* = 0.002)
- \downarrow insulinemia (-34.08 ± 7.12%, P = 0.006)
- \downarrow plasma total cholesterol (-8.68 ± 2.38%, P = 0.02)
- \downarrow body weight (-2.27 ± 0.92 kg, P = 0.091)

Pilot study, insufficient power for clinical endpoints, but interesting findings with novel microbe

Summary of postbiotic efficacy trials in adults populations - through 2021 See Table 2

Table 2 E x	Table 2 Examples of postbiotic use in adults							
Country/ region	Participants (n)	Intervention and control group	Duration of the intervention	Main conclusion				
Inactivated	Inactivated bacteria							
Italy	Helicobacter pylori-positive individuals (n = 120)	Triple therapy based on rabeprazole, clarithromycin and amoxicillin vs the same regimen supplemented with a lyophilized and inactivated culture of <i>L. acidophilus</i>	7 days	Eradication rates: triple therapy alone, 72%; triple therapy plus inactivated L . acidophilus, 87% (P = 0.02)				
France	Patients with IBS with diarrhoea ($n = 297$)	Lacteol (inactivated <i>L. acidophilus</i> LB plus fermented culture medium), two capsules daily (no control)	1 month	Improved scores for pain, bloating, frequency of diarrhoea and quality of life				
Germany	Patients with IBS ($n = 443$)	Non-viable, heat-inactivated Bifidobacterium bifidum MIMBb75 (SYN-HI-001) 1 × 10 ⁹ daily vs placebo	8 weeks	Composite primary end point of ≥30% improvement in pain and adequate relief of overall IBS symptoms in at least 4 of 8 weeks of treatment; primary end point achieved in 34% in active group vs 19% in the placebo group				
China	Patients with chronic diarrhoea ($n = 137$)	Heat-killed <i>L. acidophilus</i> LB (Lacteol Fort), two capsules BID vs lacidophilin, five chewable tablets TID	4 weeks	Reduced stool frequency at weeks 2 and 4; overall symptoms improved at 4 weeks in Lacteol group				
UK	Patients with obstructive jaundice ($n = 25$)	Oatmeal drink containing Lactiplantibacillus plantarum (formerly known as Lactobacillus	4 days	Measured intestinal permeability increased in water and inactivated groups;				





Clinical endpoints of recent (2022-2025) postbiotic studies

RCTs

Postbiotics as defined as inactivated microbes (not metabolites)

Registered trials

- Cardiometabolic markers in obese subjects*
- Diarrhea in subjects with chronic diarrhea*
- GI symptoms and mood*
- GI symptoms
- IBS (compared to live probiotic)*
- *H. pylori* eradication with antibiotics*
- Muscle strength in elderly*
- Acid reflux*
- Cold symptoms*

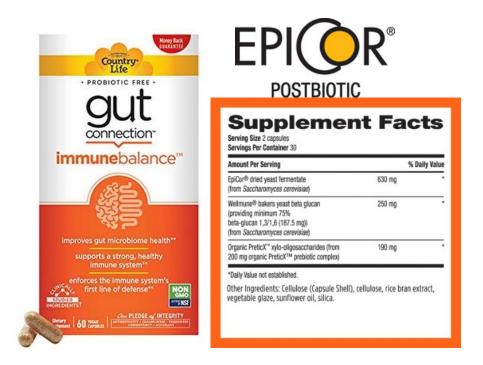
*improvement compared to control/placebo

Postbiotic medicinal products

Anti-diarrheal heat-killed *L. acidophilus* LB

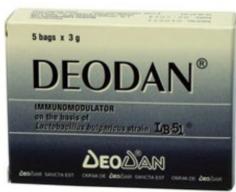


Immunomodulatory - gut microbiome balance dried yeast fermentate



Postbiotic foods?

Immunomodulatory lysozyme lysate of $L.\ bulgaricus\ LB51$

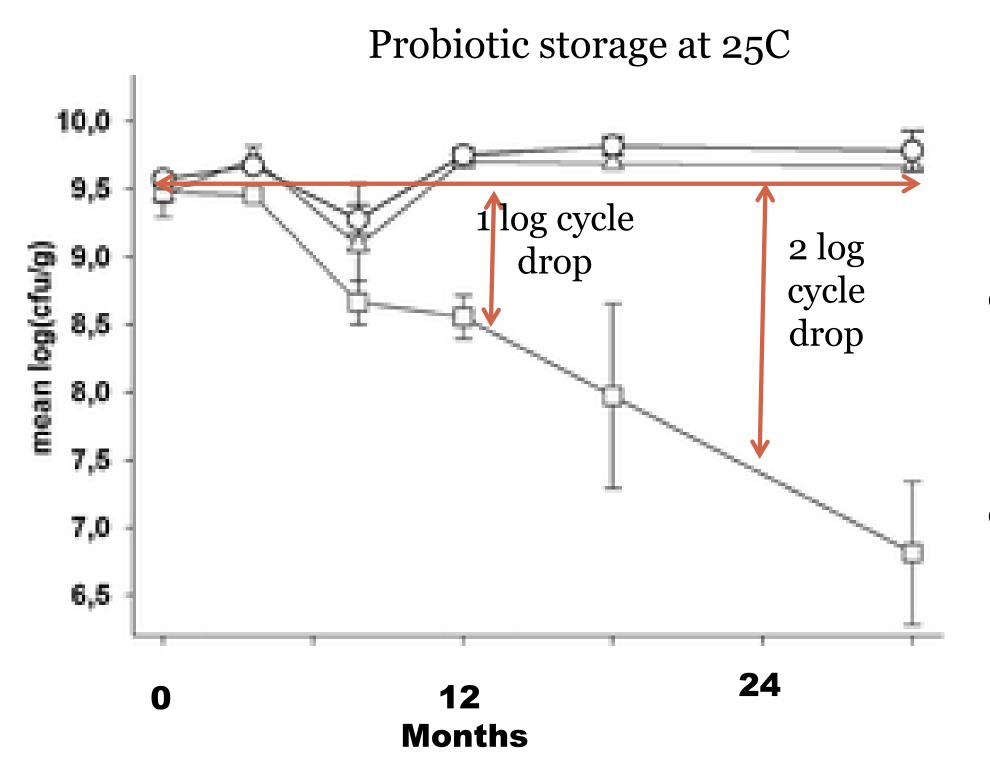


Immunomodulator based on Lactobacillus Bulgaricus strain LB51®

Bacterial antigens obtained from *S. pneumoniae* type 3, *S. pyogenes* group A, *B. catarrhalis*, *S. aureus*, *H. influenzae* type b and K



How does the concept of postbiotics impact our thinking of probiotics?



90% of "probiotic" is dead cells after 12 months

99% of "probiotic" is dead cells after 24 months

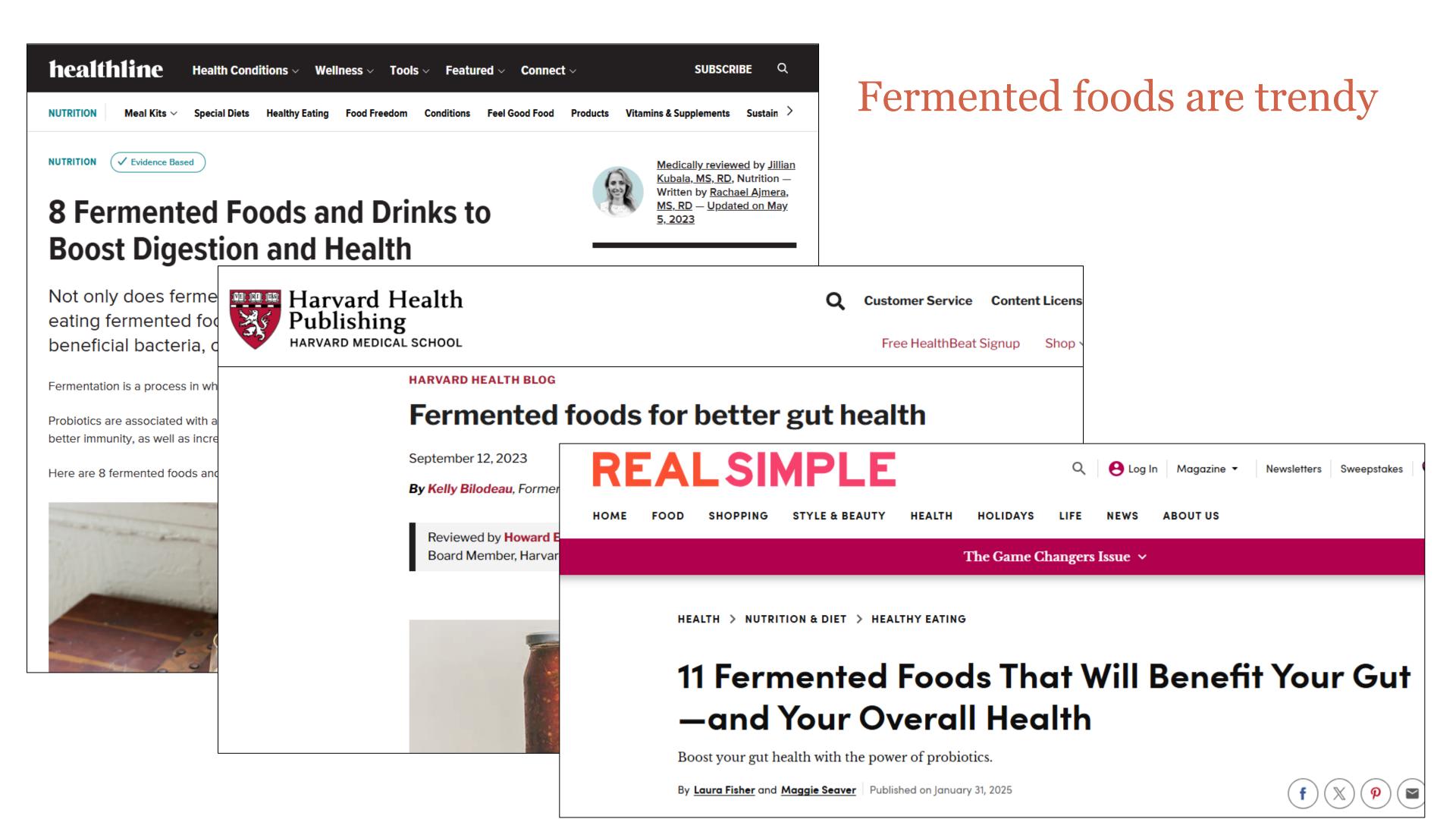
Postbiotics expand our thinking about the potential advantages to dead microbes

Do dead microbes in a probiotic have activity?

Do dead microbes in yogurt used in cooking have activity?

Not all dead microbes are postbiotics, but the potential is there

Slide courtesy of Dr. Gabriel Vinderola



Do fermented foods deliver postbiotics?

Fermented foods: a perspective on their role in delivering biotics

Gabriel Vinderola1*, Paul D. Cotter2, Miguel Freitas3, Miguel Gueimonde⁴, Hannah D. Holscher⁵, Patricia Ruas-Madiedo⁴, Seppo Salminen⁶, Kelly S. Swanson⁷, Mary Ellen Sanders⁸ and Christopher J. Cifelli⁹



frontiers Frontiers in Microbiology



Example: Sauerkraut

Contains fibers, live microbes, dead microbes, fermentation metabolites



Example: Yogurt

Contains live microbes, dead microbes, fermentation metabolites

But does that mean that it contains probiotics, prebiotics or postbiotics?

Probiotics, prebiotics and postbiotics must be fully characterized, and studies must show that they have a health benefit. This level of information often not known for traditional fermented foods.

- Encourage fermented food consumption
- Recognize the potential as delivery vehicles for biotics
- But don't overpromise on their benefits. Much remains to be learned.

But SOME fermented foods DO contain probiotics

Fermented foods MAY contain probiotics

Look for specific probiotic strain listed on label

Yogurt



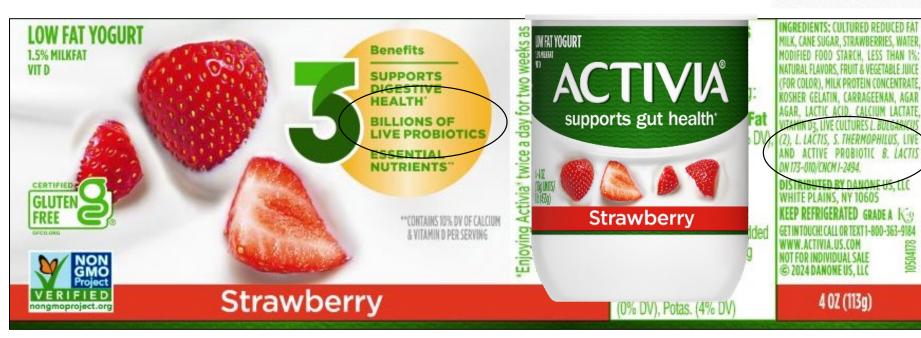
NUTRITION INFORMATION Organic Whole Milk Greek Yogurt Plain INGREDIENTS Organic Pasteurized Whole Milk, Organic Pasteurized Nonfat Milk, Organic Cream, LIVE YOGURT CULTURES: S.thermophilus. L.bulgaricus. LIVE PROBIOTIC CULTURES: Bifidobacterium lactis BB12®. L.acidophilus LA-5®, L.rhamnosus LB3. L.casei (2 isolated strains). L. rhamnosus (2 isolated strains), L. acidophilus (2 isolated strains). Bifidobacterium lactis (2 isolated strains).



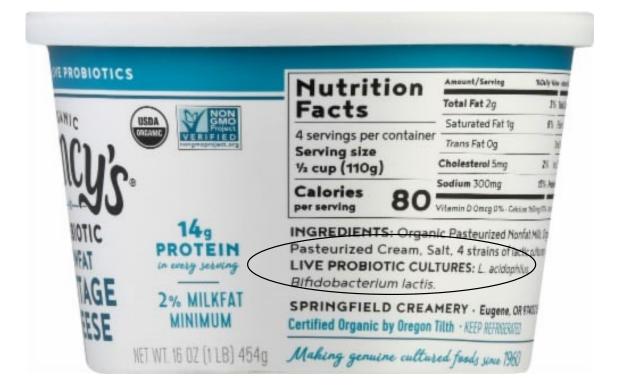
BB-12® and LA-5® are registered trademarks of Chr. Hansen

Kefir





Cottage cheese



Cultured milk

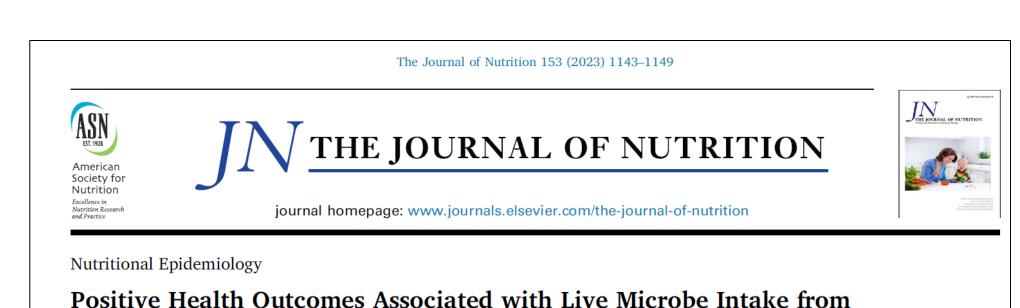


Isn't eating fermented foods a good thing?

Yes!

But recognize that we don't have causal data proving health benefits
– beyond nutritional - on most fermented foods

Data are emerging



Foods, Including Fermented Foods, Assessed using the NHANES Database

Colin Hill ^{1,†}, Daniel J. Tancredi ^{2,†}, Christopher J. Cifelli ³, Joanne L. Slavin ⁴, Jaime Gahche ⁵, Maria L. Marco ⁶, Robert Hutkins ⁷, Victor L. Fulgoni III ⁸, Daniel Merenstein ⁹, Mary Ellen Sanders ^{10,*}

Messages for your clients about postbiotics

- Postbiotics is an exciting new development, but clinical data especially for foods is emerging
- Each postbiotic is different and you cannot generalize that 'ALL postbiotics do X, Y or X'
- If clients ask you about a specific postbiotic, tell them you'll get back to them after you can verify there is evidence of a health benefit for that specific product
- Fermented foods can be nutritious components of a diet and may deliver live and dead microbes and fibers, but their role in promoting health beyond nutrition is often unknown.
- Encourage consumption of traditional fermented foods, but don't overpromise on their benefits. Much remains to be learned.

Messages for your clients about postbiotics

- Internet hype abounds
 - Searches of 'postbiotics' leads to many disparate definitions
 - Rely on high quality science, not Wikipedia-like sources, or worse
 - Incorrect information such as 'fermented foods are the best source of probiotics' is common
- Definitions matter if terms are not used rigorously, they lose all meaning
- The 'biotics' field is evolving. First probiotics, then prebiotics (and synbiotics), now postbiotics.
- All these terms refer to dietary substances that operate on the 'stage' of your gut microbiome.
- They all must be well-defined/characterized and must be shown to have a health benefit.
 - A good hypothesis is NOT the same as a documented health benefit

Questions?