

*Shared responsibility for Industry,
Regulators and Press:
What to do to get the consumer
correctly informed on probiotics?*



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Declaration of interests



- Guest professor @ the Vrije Universiteit Brussel, Brussels, Belgium

- Director of Science @ Yakult Europe BV, Almere, The Netherlands
- President of the Pharmabiotic Research Institute (PRI), Narbonne, France

The presentation flow



Complexity of the probiotic field Where health and disease come together

Regulation

Food versus pharma

Nutrition controversy

It is not exceptional in the nutrition field

Has it accelerated and spread because of social media?

The solution

The roles of

- Industry
- Regulators
- Governments
- Researchers
- Press
- Consumers

The complexity of probiotic research

The numbers

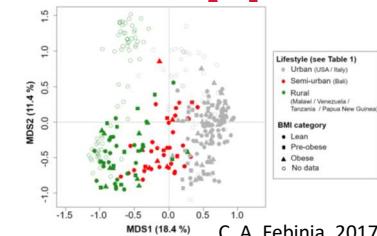
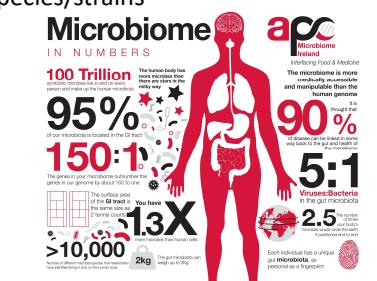
- Our gut microbiota contains 38×10^{12} microorganisms; 200 species
- A typical probiotic administration is +/- 10^9 microorganisms; one to a few species/strains
- We swallow 10^{10} microorganisms / day with our saliva

The persons

- Each of us has an individual microbiota composition
- Eating a different diet with different composition and quantity, at different times of the day
- Each is prone to different and varying levels of physical and mental stress
- With different and varying health or disease status
- With different life styles

The products

- Single versus multispecies
- Different dose and viability
- Different administration modes
- Different matrix and preservation modes
- With or without prebiotic



C. A. Febinia, 2017

The complexity of probiotic trials



The endpoint diversity

- Making it the most “powerful medicine” ever (?), influencing our microbiology, digestion, metabolism, immune and endocrine systems, brain, mood, ...
- Through a wide variety of mechanisms, mostly working simultaneously...

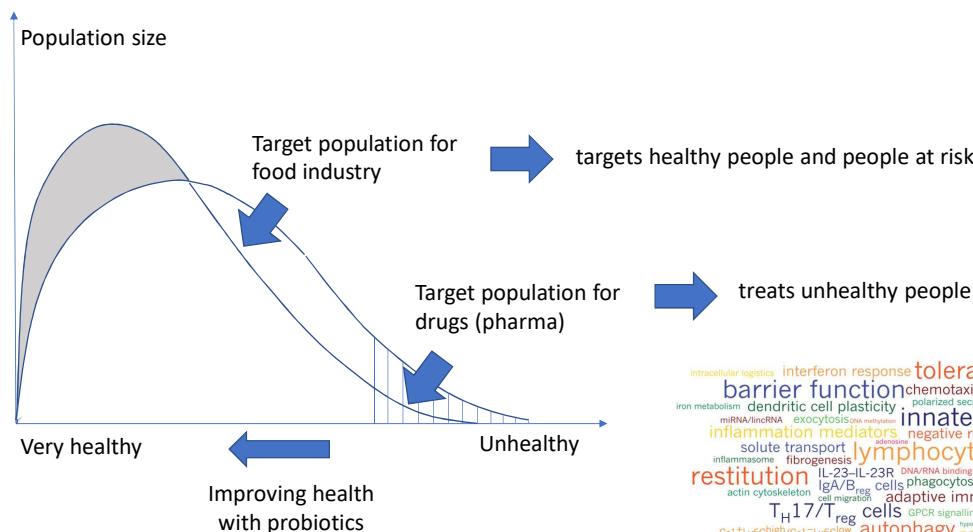
The confounding factors

- Age, smoking, compliance, geography, season, drug use (AB), ...

The health status of the subject

- Food related claims, need to be shown in a “healthy population”: how to proof a health claim in an already healthy population? How to define “health” anyhow?
- Medical claims can cure or prevent disease
- Immediate effects or results later in life ? (Ca-absorption and osteoporosis)

Probiotics: where health and disease come together



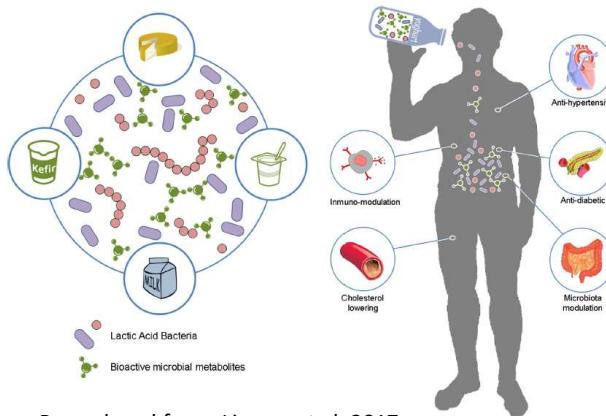
intracellular logistics interferon response tolerance carbohydrate metabolism
 barrier function chemotaxis solute carrier
 iron metabolism dendritic cell plasticity polarized secretion microtubules/centrosome
 miRNA/linRNA exocytosis adenosine
 inflammation mediators negative regulators of immunity
 solute transport fibrogenesis innate defence
 inflammasome Paneth cells
 restitution IL-23-IL-23R DNA/RNA binding antimicrobial peptides
 actin cytoskeleton IgA/B₂ cells phagocytosis adaptive immunity regulators
 T_H17/T_{reg} cells GPCR signalling ROS ER stress
 Gr1^{hi}Ly6Chigh/Ly6C^{low} IgM/IgG autophagy hypoxia
 antigen presentation lipid metabolism pathogen sensing
 stress response signature NF-κB activation/inhibition
 mycobacteria restriction factors

Modified from: Green and van der Ouderaa, 2003.

Probiotics: can they fulfil the expectation?



Health and disease is not a matter of "either/or", there is a continuum (Rijkers et al. 2010)



Reproduced from: Linares et al, 2017

NEED to MANAGE the EXPECTATIONS

Consumers are increasingly more health conscious with respect to their food:

- elderly trying to grow old(er) in a healthy, trouble-less way
- parents trying to raise their children in an optimal, healthy way and willing to pay for it
- teenagers that appreciate safe, transparently and sustainably grown food

They tend to compensate their 'fast-food behavior' or overweight with e.g. 'light products', or products enriched with probiotics, vitamins, anti-oxidants, polyphenols or omega 3, 6 ...

Their expectations, however, may be unrealistic, leading to disappointment and negative messages on social media and in the press. Education is crucial here.

Probiotics used for (too?) many applications



EDUCATION

Possible distribution of mechanisms among probiotics. Some mechanisms might be widespread among commonly studied probiotic genera; others might be frequently observed among most strains of a probiotic species; others may be rare; and others might not be present among all strains of the same species.

Evidence is accumulating on a cross-section of probiotic strains that suggest some generalizations can be made beyond strain-specific effects.

Rare Strain-specific effects

- Neurological effects
- Immunological effects
- Endocrinological effects
- Production of specific bioactives

Frequent Species-level effects

- | | |
|-----------------------------|---------------------------------|
| ▪ Vitamin synthesis | ▪ Bile salt metabolism |
| ▪ Direct antagonism | ▪ Enzymatic activity |
| ▪ Gut barrier reinforcement | ▪ Neutralization of carcinogens |

Widespread Among studied probiotics

- | | |
|------------------------------------|---|
| ▪ Colonization resistance | ▪ Normalization of perturbed microbiota |
| ▪ Acid and SCFA production | ▪ Increased turnover of enterocytes |
| ▪ Regulation of intestinal transit | ▪ Competitive exclusion of pathogens |

ALL STAKEHOLDERS

Hill et al., 2014; nature reviews

Gastroenterology & Hepatology

The presentation flow



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The role of the regulator



Functional food

PROBIOTICS

Drug (medication)

Functionality
(health) claim

- high in ...
- source of...
- improves ...
- maintains ...

Medical (Curing or
Risk reduction) claim

- prevents ...
- cures ...



The labyrinth of regulations relevant for probiotics

Category	Definition	Reference
Probiotics	The live microorganisms which when administered in adequate amounts confer a health benefit on the host.	FAO/WHO. Guidelines for the evaluation of probiotics in food. http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf
Functional foods	Food that has physiological functions, including regulation of biorhythms, the nervous system the immune system and bodily defense beyond nutrient functions	Kaushik N, Kaushik D. 2010. Functional foods. Overview and global regulation. International Journal of Pharma Recent Research 2(2): 47-52.
Dietary supplements	These are intended to supplement the diet: containing one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents and also to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement.	Food and Drug Administration. Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.htm
Drugs	An article intended for the cure, mitigation, treatment, diagnosis, or prevention of disease.	Food and Drug Administration. Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.htm
Biological product	Product containing a virus, serum, or toxin applicable to the prevention, treatment, or cure of a disease.	Food and Drug Administration. Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.htm
Medical food Medical device	Products intended for external use in the dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation and is formulated to be administered under the supervision of a physician.	Food and Drug Administration. Guidance for Industry on medical foods. May 2007. http://www.cfsan.fda.gov/~dms/medguid.html
Live biotherapeutic agent LBP	A biological product that contains live organisms, such as bacteria and is applicable to the prevention, treatment, or cure of a disease or condition of human beings excluding a vaccine.	Food and Drug Administration. Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.htm
Natural health products	It is defined as a substance, or a combination of substances, a homeopathic medicine or a traditional medicine, that is intended to provide a pharmacological activity or other direct effect in:	Canada Gazette (2003) Natural Health Products Regulations. http://gazettegc.ca/archives/p2/2003/2003-06-18/html/sor-dors196-eng.html
Novel Foods	◆ diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physiological state or its symptoms in humans ◆ restoring or collecting organic functions in humans, or ◆ modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.	Modified from Arora & Baldi, 2015 Indian J Med Microbiol

Country	Category	Definition as per country	Regulatory body
Japan	Probiotics	The live micro-organisms which when administered in adequate amounts confer a health benefit on the host	FAO/WHO
Japan	Functional foods and nutraceuticals	As per Japanese system, these products are in distinct category named as Food for Specified Health Use, with a specific regulator)' approval process separate from food fortified with vitamins, minerals, and dietary supplement not carrying FOSHU claims	MHLW, FOSHU
Europe	Functional foods	Nutraceuticals are defined as parts of a food or whole food that have any medical or health benefit, including the prevention and treatment of disease. Vitamins, minerals and herbal supplements are considered under this category.	FUFOSE
China	Functional foods	Functional food is defined as a food that has special health functions or is able to supply vitamins or minerals and has the capability to regulate human body functions	SFDA
Brazil	Functional foods	Functional foods constitute items to which health ingredients are added due to which have specific physiological function and or are enhanced with added ingredients not normally found in the product, providing health benefits beyond their nutritional value	ANVISA
New Zealand and Australia	Functional foods	Functional foods are products which are supposed to serve physiological roles beyond the provision of simple nutrient requirements	FSANZ
USA	Dietary supplements	Dietary supplements are intended to supplement the diet: containing one or more dietary ingredients (including vitamins: minerals: herbs or other botanicals: amino acids: and other substances) or their constituents and also to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement	DSHEA
USA	Drugs	Drug is an article intended for the cure, mitigation, treatment, diagnosis, or prevention of disease	FDA
USA	Biological product	Biological product is a product containing a virus, serum, or toxin applicable to the prevention, treatment, or cure of a disease	BLA
USA	Medical food	Medical food are those products intended for external use in the dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation and is formulated to be administered under the supervision of a physician	FDA
USA	Live biotherapeutic agent	Live biotherapeutic agent is a biological product; (1) contains live organisms, such as bacteria; (2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings and (3) is not a vaccine	FDA
India	Functional foods, drugs	Food that has physiological functions , including regulation of biorhythms. the nervous system, the immune system and bodily defense beyond nutrient functions	FSSA, PFA, FDA
Malaysia	Functional foods	Currently no official definition available for functional food products in Malaysia	FSQD, Drug Control Authority, NPCB and Committee for the Classification of Food-Drug Interface Products
Canada	Natural health products	It is defined as a substance, or a substances, a homeopathic medicine or a traditional medicine, that is intended to provide a pharmacological activity or other direct effect in: Diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physiological state or its symptoms in humans; Restoring or collecting organic functions in humans, or Modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health	Natural Health Products Directorate

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Europe	Functional foods		FUFOSE
China	Functional foods		SFDA
Brazil	Functional foods		ANVISA
New Zealand and Australia USA	Functional foods		FSANZ
USA	Dietary supplements		DSHEA
	Drugs		FDA
	Biological product		BLA
	Medical food		FDA
	Live biotherapeutic agent		FDA
India	Functional foods, drugs	Food that has physiological functions , including regulation of biorhythms, the nervous system, the immune system and bodily defense beyond nutrient functions	FSAA, PFA, FDA
Malaysia	Functional foods	Currently no official definition available for functional food products in Malaysia	FSQD, Drug Control Authority, NPCB and Committee for the Classification of Food-Drug Interface Products
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Consequences for producers and researchers



Need to follow the *regulator* path for the research, determining

- Clinical trials set up and endpoints
- Research targets and objectives (mechanisms)

- Number of dossiers to prepare
- Number of administrative tasks to explore and understand
- Number of languages to use (application & communication)

Not necessarily a regulatory issue: The FMT example!



ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results

Modify Search Start Over +

236 Studies found for FMT

Also searched for **Fecal Microbiota Transplantation**, **Fecal transplant**, and **Fecal Transplantation**. See [Search Details](#)

16 May 2019

Map Search Details

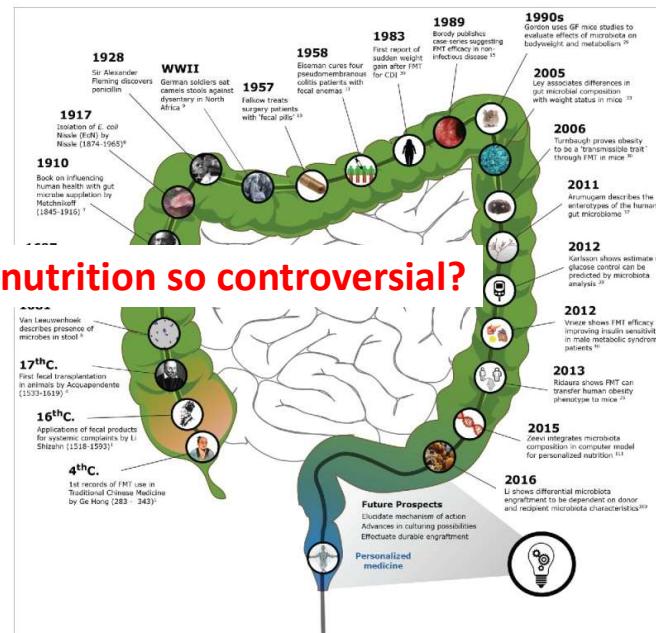
Show: 1-10 of 236 studies 10 studies per page

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Not yet recruiting	Fecal Microbiota Transplantation for Treatment of Refractory Graft Versus Host Disease-a Pilot Study	• Fecal Microbiota Transplantation in GVHD	• Biological: Fecal Microbiota Transplantation	
2	<input type="checkbox"/>	Recruiting	FMT for Patients With IBS With Fecal and Mucosal Microbiota Assessment	• Irritable Bowel Syndrome • Fecal Microbiota Transplantation	• Procedure: Fecal Microbiota Transplantation • Procedure: Sham • Procedure: Fecal and Mucosal Microbiota Assessment	• The Chinese University of Hong Kong Sha Tin, Hong Kong
3	<input type="checkbox"/>	Recruiting	Fecal Microbiota Transplant (FMT) to Induce Weight Loss in Obese Subjects	• Obesity	• Procedure: Fecal Microbiota Transplantation	• The Chinese University of Hong Kong Hong Kong, Hong Kong
4	<input type="checkbox"/>	Not yet recruiting	Autologous Fecal Microbiota Transplantation for Patients With Acute Graft-versus-Host Disease	• Fecal Microbiota Transplantation in Graft vs. Host Disease	• Biological: Autologous Fecal Microbiota Transplantation	• Rambam Health Care Campus Haifa, Israel
5	<input type="checkbox"/>	Recruiting	The Finnish Faecal Microbiota Transplantation Study (FINFMT)	• Faecal Microbiota Transplantation		• Joint Authority for Paliat-Hame Social and Health Care Lahti, Finland
6	<input type="checkbox"/>	Not yet recruiting	Fecal Microbiota Transplantation (FMT) in Treatment of Severe and Enduring Anorexia Nervosa	• Anorexia Nervosa	• Biological: Fecal Microbiota Transplantation (FMT)	• UNC Chapel Hill Chapel Hill, North Carolina, United States

The FMT example

- No initial regulation, although ...
- application in humans was based on observations from animal experiments
- Post-use regulated in a number of countries (treated as Drug or as Human Tissue)
- Application list is expanding without too much regulatory problems (C. dif; Metab. Syndr., Obesity, IBD, ...)
- Like probiotics: Sometimes successful, sometimes not!!!

Why is nutrition so controversial?



P. F. de Groot, M. N. Frissen, N. C. de Clercq, and M. Nieuwdorp; Gut Microbes. 2017.

The presentation flow



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- Governments
- Researchers
- Press
- Consumers

Ann Hum Genet. 2008 Jan;72(Pt 1):48-56. Epub 2007 Aug 7.

The Mediterranean paradox for susceptibility factors in coronary heart disease extends to genetics.

Lao O¹, Duponchou I¹, Barbujani G¹, Bertranpetti J¹, Calafell F¹,...
Medical Hypotheses
 Volume 80, Issue 2, February 2013, Pages 150-155

Mediterranean diet and the Spanish paradox hypothesis

Federico Soriano^{a,b,c}, Eva García-Escobar^{a,b,c}, R. S^a,...
 Rodriguez de Fonseca^d, Gabriel Oliveira^{a,b,c}, Gemma Rojo-Martínez^{a,b,c}

Cardiovascular Research, Volume 54, Issue 3, June 2002, Pages 503-515,
[https://doi.org/10.1016/S0008-6363\(01\)00545-4](https://doi.org/10.1016/S0008-6363(01)00545-4)

Lab-Grown Meat The Controversy
 by Yossi Krausz
 wave vegetation tendencies, there is a good chance you enjoy a juicy, flame-broiled steak. The caramelized...
 ...ion, which gives browned food its distinctive flavor, make being an omnivore enjoyable. But...
 ...meat from animals on philosophical grounds may be able to savor that same...
 ...nvironmentalists, who opine that cows are more dangerous than cars to...
 ...the matter.
 ...n quality, flavor and price—with the

SCIENCE
 Vol. 103, No. 2668
 Friday, February 15, 1946

The Butter-Margarine Controversy¹
 Harry J. Deuel, Jr.
School of Medicine, University of Southern California

TIME
 Eat Butter.
 Scientists labeled fat the enemy. Why they were wrong
 BY ROBERT WALKER

WHY IS PALM OIL SO CONTROVERSIAL?
 DAVID SAUNDERS * 22ND FEBRUARY 2013
 May 11, 2018
 Healthy Friday: The butter-versus-margarine controversy – who should you believe?
 Both butter and margarine have been bad mouthed in turns for decades, so wh...
 the truth?

**TOFU: HEART
 HEALTHY
 SUPERFOOD OR
 ENVIRONMENTAL
 NIGHTMARE?**

VUB VRIJE
 UNIVERSITEIT
 BRUSSEL

Beth Jorgensen Saginaw Valley State University

AUGUST 9, 2014 2 COMMENTS

CONCLUSION:

Why is nutrition so controversial?

What is this doing to a consumer?

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Why is nutrition so controversial?

- Is it because of the relation to health?
to the environment?
- Is it because of the social media's hunger for new material?
- Or both?

FOOD FOR THOUGHT

Catchy headlines and fake news: A case study in cultured meat

By David Burrows
12-Apr-2019 - Last updated on 12-Apr-2019 at 10:04 GMT





The search for a The search for an exciting angle or click-bait means the mass risks over-simpl media risks over-simplifying the discourses around food production

Cultured meat might not be climate friendly, but how many people read the full story?

Pressure to secure publicity for new research is fierce, so it's easy to see why the press team at the University of Oxford teed up a paper published in the journal *Frontiers in Sustainable Food Systems*, like this: "Growing meat in the laboratory may not be better for the climate in the long run than meat from cattle." It sounds a lot better than cultured meat in most scenarios seems to be better for the climate than cattle. This is the received wisdom, after all, so puncture a hole in that and you have a story.

And true to form many outlets gobbled up the findings. The BBC went with: "Cultured lab meat may make climate change worse." The Independent chose: "Lab grown meat could cause more environmental damage than the real thing, scientists warn." Most of the (widespread) coverage was in a similar vein.

However, as FoodNavigator's own coverage of the research reflected, the actual findings were a lot more nuanced than the headlines – and indeed a fair chunk of the content below them – suggested. This is nothing new, but it doesn't make it any less concerning.

Let's look at what the researchers did and what they found.

Agricultural greenhouse gas emissions are responsible for around a quarter of current global warming. Replacing conventional cattle farming with "labculture" – meat grown in the lab using cell culture – has therefore been touted as a way to impact.



Also affecting probiotics

Rao et al. *Clinical and Translational Gastroenterology* (2018) 16:2 DOI 10.1038/s41424-018-0030-7

Clinical and Translational Gastroenterology

ARTICLE Open Access

Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis

385.000 Google hits

Brain fogginess D lactic acid

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Page 2 of about 385.000 results (0,44 seconds)

Probiotics cause brain fog? - Scientific Wellness

<https://www.scientificwellness.com/blog-view/do-probiotics-cause-brain-fog-670> ▾ Sep 3, 2018 - The research paper entitled 'Brain fogginess, gas and bloating: a link ... and increase d-lactic acid production which might cause brain fog, ...

Could probiotics cause 'brain fog' and bloating? - Medical News Today

<https://www.medicalnewstoday.com/articles/322712.php> ▾ Aug 8, 2018 - The use of probiotics could lead to a cluster of symptoms — that include brain fog and abdominal bloating — by increasing bacteria in the small intestine. Might probiotics be behind severe abdominal bloating and brain fog? ... Lactobacillus bacteria species, one of "the most ...

Is kombucha healthy? It might cause brain fog | Well+Good

<https://www.wellandgood.com/good.../is-kombucha-healthy-probiotics-brain-fog/> ▾ Aug 8, 2018 - Probiotics have been linked to brain fog—so should you kick your ... When you have too much D-lactic acid, it can seep into your blood steam, ...

Brain fog, bloating, and gas: Could probiotics be to blame? - Medical ...

https://www.medicalnewsbulletin.com/latest-medical-news ▾ Sep 24, 2018 - It can also cause the release of D-lactic acid which is temporarily toxic to brain cells. High levels of D-lactic, referred to as lactic acidosis, can ...

Probiotic Supplements Might Be Giving Some People 'Brain Fog'

[https://gizmodo.com/probiotic-supplements-might-be-giving-some-people-brain-1828... ▾](https://gizmodo.com/probiotic-supplements-might-be-giving-some-people-brain-1828...) Aug 7, 2018 - Most of the brain fog group had signs of D-lactic acidosis. They also had too much bacteria in their small intestine, known as small intestinal ...

'Brain Fogginess' and D-Lactic Acidosis: Probiotics Are Not the ...

https://www.reddit.com/r/.../aaakkss/brain_fogginess_and_d_lactic_acidosis_probiotics/ ▾ Dec 29, 2018 - 4 posts · 3 authors

There's a small section of the probiotics industry that emphasizes "d-lactic acid strain free" products, likely spiraling out of the Rao study.

Do Probiotics Make IBS Worse?! Here's the bottom line on D-lactate ...

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6303722/>

Source: metamorworks/Shutterstock

recently published in the journal Clinical and Translational Gastroenterology.

August 2018

The frequency for probiotics is increasing...

September 2018

Cell

Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Jotham Suez, Niv Zmora, Gili Zilberman-Schapira, Jotham Suez, ..., Zamir Halpern, Eran Segal, Eran Elinav

Cell

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Jotham Suez, Niv Zmora, Gili Zilberman-Schapira, ..., Zamir Halpern, Eran Segal, Eran Elinav

Human gut study questions probiotic health benefits

CELL PRESS

Probiotics are found in everything from chocolate and pickles to hand lotion and baby formula, and millions of people buy probiotic supplements to boost digestive health. But new research suggests they might not be as effective as we think. Through a series of experiments looking inside the human gut, researchers show that many people's digestive tracts prevent standard probiotics from successfully colonizing them. Furthermore, taking probiotics to counterbalance antibiotics could delay the return of normal gut bacteria and gut gene expression to their naive state. **The research publishes as two back-to-back papers on September 6 in the journal Cell.** "People have thrown a lot of support to probiotics, even though the literature underlying our understanding of them is very controversial; we wanted to determine whether probiotics such as the ones you buy in the supermarket do colonize the gastrointestinal tract like they're supposed to and then whether they're actually having any impact on the microbiome," says senior author Eran Elinav, an immunologist at the Weizmann Institute of Science in Israel. "Surprisingly, we saw that many healthy volunteers were actually resistant in that the probiotics couldn't colonize their GI tracts. This suggests that probiotics should not be universally given as a 'one-size-fits-all' supplement. Instead, they could be tailored to the needs of each individual."

While past studies have investigated similar questions, they have all used patients' excrement as a proxy for microbe activity in the GI tract. Instead, Elinav, his colleague Eran Segal, (a computational biologist at the Weizmann Institute), and their teams spearheaded by Niv Zmora, Jotham Suez, Gill Zilberman Schapira, and Uria Mor of the Elinav lab collaborated with Zamir Halpern, Chief of Gastroenterology at the Tel Aviv Medical Center to measure gut colonization directly.

In the first study, 25 human volunteers underwent upper endoscopies and colonoscopies to sample their baseline microbiome in regions of the gut. 15 of those volunteers were then divided into two groups. The first group consumed generic probiotic strains, while the second was administered a placebo. Two months later, they underwent a second round of upper endoscopes and colonoscopies to assess their internal response before being followed for another 2 months.

The scientists discovered that the probiotics successfully colonized the GI tracts of some people, called the "persisters," while the gut microbiomes of "resisters" expelled them. Moreover, the persister and resister patterns would determine whether probiotics, in a given person, would impact their indigenous microbiome and human gene expression. The researchers could predict whether a person would be a persister or resister just by examining their baseline microbiome and gut gene expression profile. They also found that stool only partially correlates with the microbiome functioning inside the body, so relying on stool as was done in previous studies for many years could be misleading.

"Although all of our probiotic-consuming volunteers showed probiotics in their stool, only some of them showed them in their gut, which is where they need to be," says Segal. "If some people resist and only some people permit them, the benefits of the standard probiotics we all take can't be as universal as we once thought. These results highlight the role of the gut microbiome in driving very specific clinical differences between people."

In the second study, the researchers questioned whether patients should be taking probiotics to counter the effects of antibiotics, as they are often told to do in order to repopulate the gut microbiota after it's cleared by antibiotic treatment. To look at this, 21 volunteers were given a course of antibiotics and then randomly assigned to one of three groups. The first was a "watch-and-wait" group that let their microbiome recover on its own. The second group was administered the same generic probiotics used in the first study. The third group was treated with an autologous fecal microbiome transplant (aFMT) made up of their own bacteria that had been collected before giving them the antibiotic.

After the antibiotics had cleared the way, the standard probiotics could easily colonize the gut of everyone in the second group, but to the team's surprise, this probiotic colonization prevented the host's normal microbiome and gut gene expression profile from returning to their normal state 2 months afterward. In contrast, the aFMT resulted in the third group's native gut microbiome and gene program returning to normal within days.

"Contrary to the current dogma that probiotics are harmless and benefit everyone, these results reveal a new potential adverse side effect of probiotic use with antibiotics that might even bring long-term consequences," Elinav says. "In contrast, replenishing the gut with one's own microbes is a personalized mother-nature-designed treatment that led to a full reversal of the antibiotics' effects."

Segal adds, "This opens the door to diagnostics that would take us from an empiric universal consumption of probiotics, which appears useless in many cases, to one that is tailored to the individual and can be prescribed to different individuals based on their baseline features."

###

Very unlikely, whereas it's simple

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The frequency for probiotics is increasing...

BBC NEWS

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Human gut study questions probiotic health benefits

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Probiotics are found in everything from chocolate and pickles to hand lotion and baby formula, and millions of people buy probiotic supplements to boost digestive health. But new research suggests they might not be as effective as we think. Through a series of experiments looking inside the human gut, researchers show that many people's digestive tracts prevent standard probiotics from successfully colonizing them. Furthermore, taking probiotics to counterbalance antibiotics could delay the return of normal gut bacteria and gut gene expression to their naive state. **The research publishes as two back-to-back papers on September 6 in the journal Cell.** "People have thrown a lot of support to probiotics, even though the literature underlying our understanding of them is very controversial; we wanted to determine whether probiotics such as the ones you buy in the supermarket do colonize the gastrointestinal tract like they're supposed to and then whether they're actually having any impact on the microbiome," says senior author Eran Elinav, an immunologist at the Weizmann Institute of Science in Israel. "Surprisingly, we saw that many healthy volunteers were actually resistant in that the probiotics couldn't colonize their GI tracts. This suggests that probiotics should not be universally given as a 'one-size-fits-all' supplement. Instead, they could be tailored to the needs of each individual."

While past studies have investigated similar questions, they have all used patients' excrement as a proxy for microbe activity in the GI tract. Instead, Elinav, his colleague Eran Segal, (a computational biologist at the Weizmann Institute), and their teams spearheaded by Niv Zmora, Jotham Suez, Gill Zilberman Schapira, and Uria Mor of the Elinav lab collaborated with Zamir Halpern, Chief of Gastroenterology at the Tel Aviv Medical Center to measure gut colonization directly.

In the first study, 25 human volunteers underwent upper endoscopies and colonoscopies to sample their baseline microbiome in regions of the gut. 15 of those volunteers were then divided into two groups. The first group consumed generic probiotic strains, while the second was administered a placebo. Two months later, they underwent a second round of upper endoscopes and colonoscopies to assess their internal response before being followed for another 2 months.

The scientists discovered that the probiotics successfully colonized the GI tracts of some people, called the "persisters," while the gut microbiomes of "resisters" expelled them. Moreover, the persister and resister patterns would determine whether probiotics, in a given person, would impact their indigenous microbiome and human gene expression. The researchers could predict whether a person would be a persister or resister just by examining their baseline microbiome and gut gene expression profile. They also found that stool only partially correlates with the microbiome functioning inside the body, so relying on stool as was done in previous studies for many years could be misleading.

"Although all of our probiotic-consuming volunteers showed probiotics in their stool, only some of them showed them in their gut, which is where they need to be," says Segal. "If some people resist and only some people permit them, the benefits of the standard probiotics we all take can't be as universal as we once thought. These results highlight the role of the gut microbiome in driving very specific clinical differences between people."

In the second study, the researchers questioned whether patients should be taking probiotics to counter the effects of antibiotics, as they are often told to do in order to repopulate the gut microbiota after it's cleared by antibiotic treatment. To look at this, 21 volunteers were given a course of antibiotics and then randomly assigned to one of three groups. The first was a "watch-and-wait" group that let their microbiome recover on its own. The second group was administered the same generic probiotics used in the first study. The third group was treated with an autologous fecal microbiome transplant (aFMT) made up of their own bacteria that had been collected before giving them the antibiotic.

After the antibiotics had cleared the way, the standard probiotics could easily colonize the gut of everyone in the second group, but to the team's surprise, this probiotic colonization prevented the host's normal microbiome and gut gene expression profile from returning to their normal state 2 months afterward. In contrast, the aFMT resulted in the third group's native gut microbiome and gene program returning to normal within days.

"Contrary to the current dogma that probiotics are harmless and benefit everyone, these results reveal a new potential adverse side effect of probiotic use with antibiotics that might even bring long-term consequences," Elinav says. "In contrast, replenishing the gut with one's own microbes is a personalized mother-nature-designed treatment that led to a full reversal of the antibiotics' effects."

Segal adds, "This opens the door to diagnostics that would take us from an empiric universal consumption of probiotics, which appears useless in many cases, to one that is tailored to the individual and can be prescribed to different individuals based on their baseline features."

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Very unlikely, whereas it's simple

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The frequency for probiotics is increasing...

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Human gut study questions probiotic health benefits
Probiotics are found in everything from chocolate and pickles to hand lotion and baby formula, and millions of people buy probiotic supplements

Surprisingly, we saw that many healthy volunteers were actually resistant in that *the probiotics couldn't colonize their GI tracts*. This suggests that probiotics should not be universally given as a 'one-size-fits-all' supplement. **What is New Here?**

"**Although all of our** **Why all the fuzz?** **ers showed probiotics in their stool, only some of them showed them in their** **gut**, which is where they need to be," "If some people resist and only some people permit them, the benefits of the standard probiotics we all take can't be as universal as we once thought." **Many MDs world-wide** **will disagree!**

"Although all of our probiotic-consuming volunteers showed probiotics in their stool, only some of them showed them in their gut, which is where they need to be," says Segal. "If some people resist and only some people permit them, the benefits of the standard probiotics we all take can't be as universal as we once thought." **So we simply deposit our poo**

"In contrast **before we go on ABs or ...** **personalized** **become coprophagic?**"

A group of scientists in Israel claim foods that are packed with good bacteria - called probiotics - are almost useless.

Probiotics include yogurts that contain "good bacteria".

... while probiotics may have potential economic benefits

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- 70% of the US population is overweight
- 38% of the US population is obese
- 10% of the US population is diabetic

Original article: Lin Yang & Graham A. Colditz
Prevalence of Overweight and Obesity in the United States, 2007-2012. JAMA Intern Med. 2015;175(8):1412-1413.

Gender	Normal or below	Overweight	Obese
WOMEN	30%	37%	33%
MEN	40%	35%	25%

<https://www.toledoblade.com/Food/2015/06/23/70-of-Americans-overweight-or-obese-study-finds.html>

What if all the French ate probiotics?



King et al.:

- 2.4 million fewer days with RTI
- 291 000 fewer courses of antibiotics
- 581 000 fewer days sick leave

British Journal of Nutrition,

Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis

Sarah King¹, Julie Glanville^{1*}, Mary Ellen Sanders², Anita Fitzgerald¹ and Danielle Varley¹

Hao et al. :

- 6.6 million fewer days with RTI
- 473 000 fewer courses of antibiotics
- 1 453 000 fewer days sick leave

Probiotics for preventing acute upper respiratory tract infections (Review)

Hao Q, Lu Z, Dong BR, Huang CQ, Wu T

[PLoS One](#). 2015; 10(4): e0122765.

Published online 2015 Apr 10. doi: [10.1371/journal.pone.0122765](https://doi.org/10.1371/journal.pone.0122765)

PMCID: PMC4393230

PMID: 25859849

Public Health and Budget Impact of Probiotics on Common Respiratory Tract Infections: A Modelling Study

Irene Lenoir-Wijnkoop,^{1,2,*} Laetitia Gerlier,³ Jean-Louis Bresson,⁴ Claude Le Pen,⁵ and Gilles Berdeaud,^{3,6}

How does this compare?



- Better than vitamin C (RR=0.97)
- Similar as hand washing (OR=0.54)
- Similar than neuramidase inhibitors (-0.7 days)
- Worse than gloves, masks and gowns (OR=0.32)

The presentation flow



Complexity of the probiotic field

Where health and disease come together

Regulation

Food versus pharma

Nutrition controversy

It is not exceptional in the nutrition field

Has it accelerated and spread because of social media?

The solution

The roles of

- Industry
- Regulators
- Governments
- Researchers
- Press
- Consumers

The role of the industry.



- Industry should keep investing in high quality research, develop new food products with increased nutritional and/or health promoting properties.
- They should be clear on the use of the products they bring on the market, whether as food, food supplement, medical food or drug, in order not to confuse the consumer.
- Quality criteria for e.g. probiotic products should always be met (safety, sufficient numbers at the end of the shelf-life, viability after the GIT passage, and functionality as demonstrated by clinical trials).

Industry initiatives



The IPA criteria used to define a “probiotic” encompass 4 requirements:

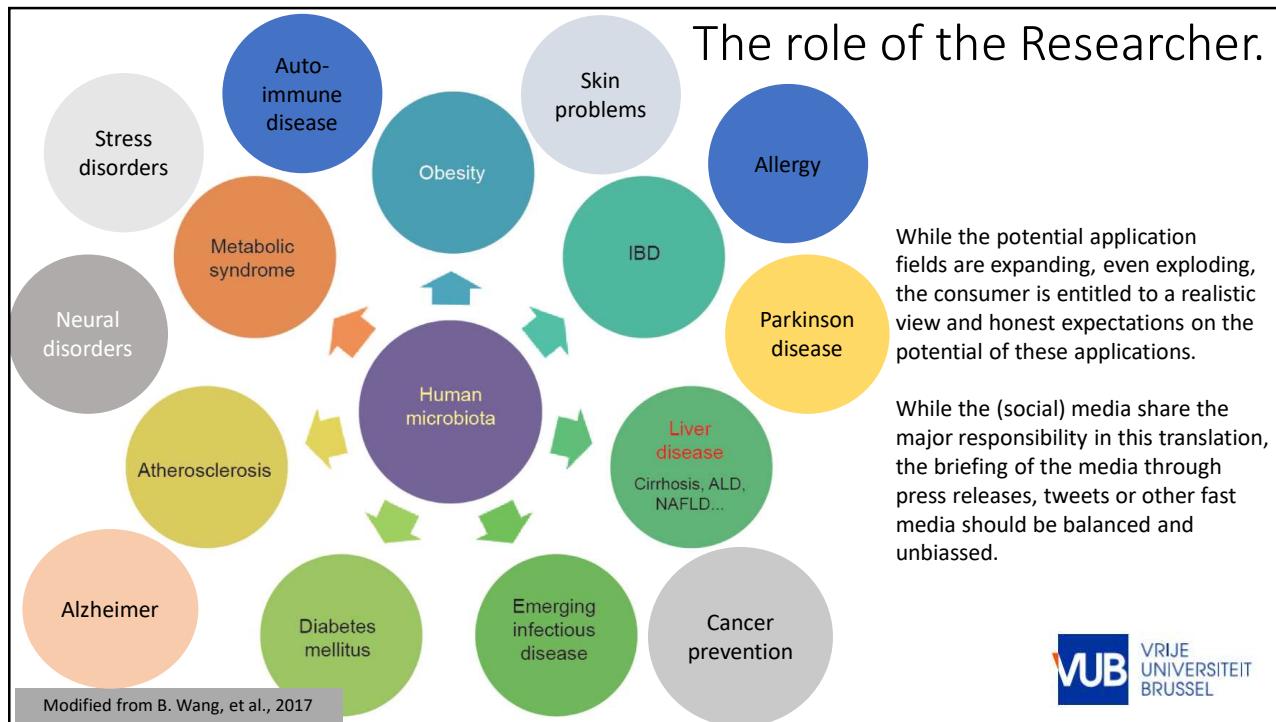
- 1) taxonomic characterized at the species level and identifiable at the strain level;
- 2) safe for the intended use;
- 3) the probiotic status must be scientifically documented by at least one supportive human clinical study, according to generally accepted scientific standards;
- 4) must be alive in the product and in a sufficient amount to achieve the desired effect up to the end of shelf-life and when consumed.
- The ISAPP has defined similar criteria and added the need for the deposit of the strain in an international culture collection.
(<https://isappscience.org/minimum-criteria-probiotics/>)
- In December of 2017 IPA presented a proposal to *Codex Alimentarius* regarding the establishment of guidelines for probiotic foods. *Codex Alimentarius* accepted this proposal and requested that Argentina prepare draft guidelines. These will be considered in the 2019 session of the *Codex Alimentarius* Committee on Nutrition and Foods for Special Dietary Use.

The role of the Researcher.



- The researcher should use established technologies
- Remain independent as academic authority and report in an unbiased way
- The peer reviewing process is critical for any publication, but should also be unbiased and transparent
- In this way results will be published in high level journals and match homologous research from e.g. the medical field





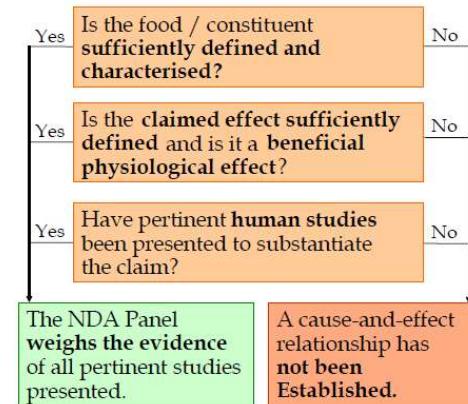
The role of the Media.



- All media should communicate in a realistic, non-skewed and balanced way on new research.
- As the communication concerns health aspects, the consumer is definitely in need of scientifically correct and balanced information, referring both to benefits and risks, so he can weigh the new info with existing and established science.
- Bloggers should refrain from commenting in a field that is not in their expertise, especially when health issues are concerned.
- ‘Lack of time to verify’ cannot be an excuse to publish fake or unchecked news, especially when health issues are concerned.
- The use of logo’s or brand names should only be used if they are really concerned, both for bad and good news.

The role of the regulator.

- Regulators should define feasible criteria allowing recognition of the research efforts.
- The evaluation should be done in the spirit of the category concerned and not be more severe for foods than e.g. for pharmaceutical products or clinical practices (FMT example)



EFSA HC evaluation scheme

EFSA 2011a; General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal. 9(4): 2135. (doi:10.2903/j.efsa.2011.2135)

The role of the food regulator.

- The regulator should try to clarify and simplify the status of probiotic-based products by clearing all current ambiguities
- Various regulatory agencies in different countries should preferably adhere to a single definition and limit the category descriptions for probiotics (Codex?)
- The regulator should define the appropriate level of evidence for determining a health benefit for probiotics and should put safety and functionality ahead of commercial interests.
- However, they should also be flexible to absorb new science and developments when proper scientific evidence is provided (FMT case).



The role of the Governments.

- Control of compliance for the true probiotics
- Policing the 'cowboy' products
- Assisting and insisting regulators for a fair regulation that
 - Protects the consumer
 - Stimulates industry to innovate in new products and applications



CODEX ALIMENTARIUS

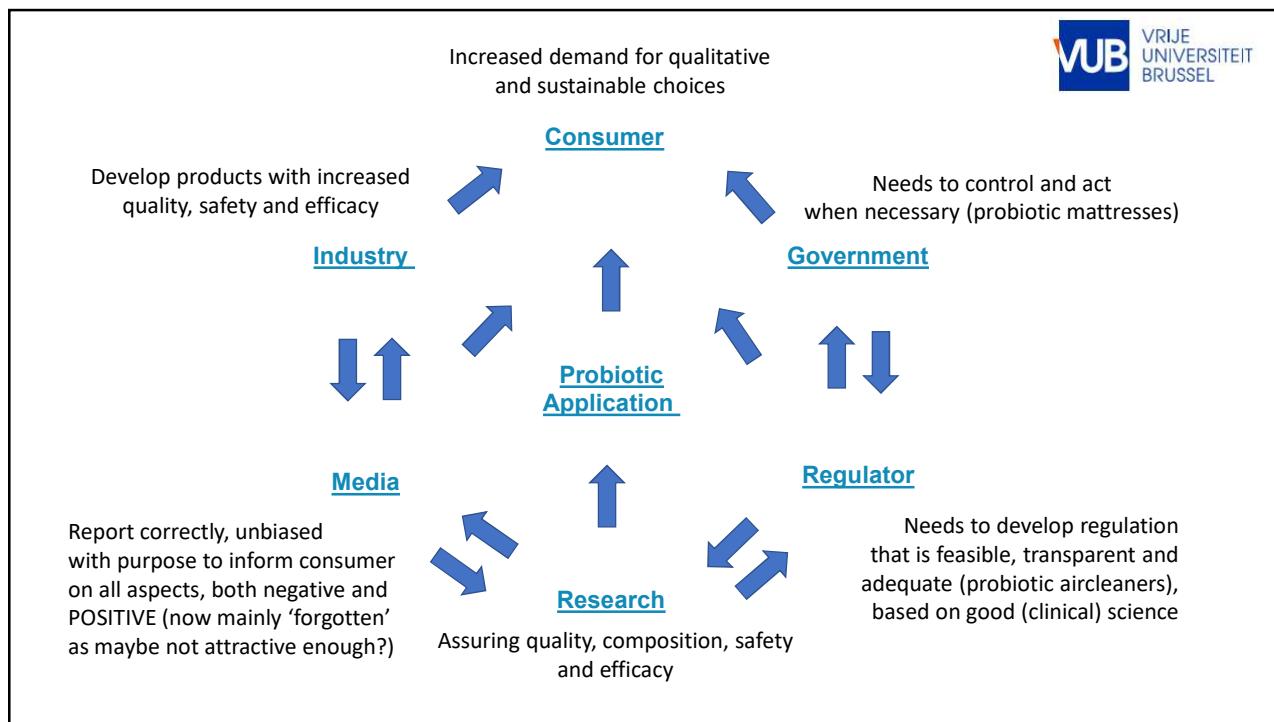
INTERNATIONAL FOOD STANDARDS



The role of the Consumer.



- Consumers are more demanding regarding the quality of their food, but they should remain realistic regarding the potential of dietary supplements or functional foods.
- They are rightly looking for optimal ways to get the nutrients and compounds that they need, preferably produced via a natural and sustainable approach.
- They should realize, however, that there is a cost involved in the development of these products and there can be limits to their requirements. Certain levels of processing and packaging may be necessary for safety or functionality reasons.
- They should be critical as to the information they receive through social media and they should consult multiple, reliable sources to obtain a balanced answer to their question.



The solution?

**Let your food be your medicine.
Your medicine your food.**

Hippocrates' wisdom from the past

