Microbiome friendly

Facts about PROBIOTICS

WHITE PAPER

December, 2019

Author:

Kristin Neumann, PhD

Author & Co-Founder
MyMicrobiome.info - The Microbiome Information Platform, developed the first and only standard for Microbiome friendly cosmetics and personal care products and also probiotic food supplements.

MyMicrobiome

www.MyMicrobiome.info

Your Microbiome Information Platform!

Probiotics are a hot topic at the moment and are controversially discussed. In this White Paper, all currently known facts about probiotics are summarized and all misconceptions are set straight.

Contents

I. Defintion of probiotics

The definition of probiotics was determined in 2001 jointly by the FAO (Food and Agriculture Organization of the United Nations) and the WHO (World Health Organization), then again confirmed in 2013 by the International Scientific Association for probiotics and prebiotics (ISAPP): Probiotics are ...

> ***"... live microorganisms that, when administrated in adequate amounts, confer a health benefit to the host".***

The "live microorganisms" named in this definition refer to only those ones which are precisely characterized and whose health benefits are scientifically demonstrated. Fermented products, such as sauerkraut, kimchi or kombucha, contain certain bacteria, however, they are not considered as probiotics, since they are not characterized exactly. The same applies to natural bacteria in the intestine. Only those which are supplied to the organism within food or food supplements are probiotics.

Moreover, for each probiotic, an exact strain must be specified, e.g. *Lactobacillus rhamnosus* GG. The exact strain name is very important because another *Lactobacillus rhamnosus* strain can have a completely different effect.

Gregor Reid, a very well-known researcher in the field of probiotics (former president of the ISAPP, Chair of the UN and WHO), illustrates the importance of naming the exact strain by using figurative comparisons:

"We give names to people. Because of genetics and development every person is different. [...] So, there are likely millions of men called James Smith in the world. But, what if I need the one who lives in London Ontario, who is a lawyer with twenty years' experience specializing in patenting biological compounds?

My point is, you cannot say all James Smiths are patent lawyers. Likewise, you can't say all lactobacilli or bifidobacteria are probiotics. They may have beneficial attributes but you need to prove them. For example, if you wanted a Lactobacillus *strain to improve vaginal health, you would not take* Lactobacillus rhamnosus *GG, but would take* Lactobacillus rhamnosus *GR-1, as the latter is genetically different from the former, and has genes adapted to the vagina, with clinical studies showing benefits to that area of the body. Likewise,* Bifidobacterium longum *35624 sold as Align is one option for irritable bowel syndrome but not for vaginal health.*

[...] There may also be lactobacilli in sauerkraut, but unless the strain has been tested and shown to be probiotic, and the same viable numbers are in the sauerkraut, or unless the specific product is tested (Mama Gee's Sauerkraut) you can't call the fermented food probiotic. Having James Smith is not enough. [...]."*

I. Definition of probiotics

In addition to the **precise designation** of the probiotic strain, the **correct dosage** is also essential. For each bacterial or fungal strain contained in a product, an **exact number of colony-forming units** must be specified, because probiotics, like medicines, should be administered at a certain dose. If a mixture is offered, the exact the number for each individual bacterial or fungal strains within the mixture must be evaluated.

II. Products and strains

Probiotics are available in a variety of products, often in yoghurt or yoghurt cultures but mostly in the form of capsules.

The most common probiotics are:

- *Lactobacillus*
- *Bifidobacterium*
- *Saccharomyces*
- *Bacillus*

III. The pace of life on our planet

Microbes were the first inhabitants of the earth. The first signs of microbial life have been detected in 3.86 billion years old rocks, and the Earth is approximately 4.5 billion years old.

All life on earth can be divided into three domains (the highest biological taxon):

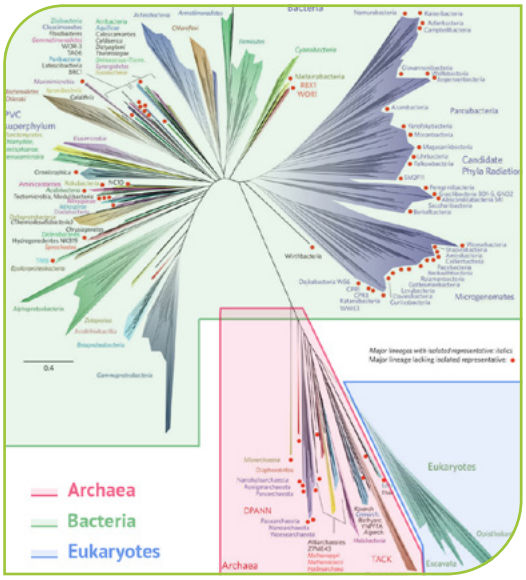
archaea, bacteria and eukaryotes.

Archaea are a very old domain. They look like bacteria, but their genes are completely different. Moreover, they have a special biochemistry. Mostly they can be found in extreme ecosystems, such as hot springs or salt lakes. However, they are also present in ecological niches such as the gut or the navel.

The **bacteria** domain currently contains 92 phyla (domain subdivisions). Thus, they are the greatest of all three domains. Alone in 2016 more than 1,000 new bacterial organisms were found, and scientists are confident that they will find even more. A bacterial cell is 10 times smaller than a human cell.

Eukaryotes are organisms with nucleus and cell organelles. They are the youngest domain. They are the building block for the complex, multicellular life that originated over 600 million years ago. Some eukaryotes also belong to microbes, for example, fungi or algae.

Archaea - can be found in extreme ecosystems.



Hug et al., A new view of the tree of life, 2016

Eukaryotes are organisms with nucleus and cell organelles.

IV. History of probiotics

Living bacteria were consumed long before bacteria were discovered.

There are old Egyptian hieroglyphic characters that refer to fermented milk products. Fermentation methods were traditionally used by Tibetan nomads for milk preservation.

It was only in the **18th century** when fermented foods began to be associated with better health, but still without any reference to bacteria. Although Louis Pasteur discovered yeasts and bacteria which initiate the fermentation process, he did not associate bacteria/yeast with health.

Then, in **1905**, Elie Metchnikoff was the first scientist who associated bacteria in yoghurt with bacteria in the gut.

In **1906**, the first *Bifidobacterium* was isolated by Henry Tissier from the gut of a child. Tissier claimed that this bacterium can displace pathogenic bacteria in the gut.

In the year **1922**, the first clinical studies were performed with *Lactobacillus acidophilus* in 30 patients who had constipation, diarrhoea and eczema. The bacterium demonstrated its healing effect on these illnesses.

In the **1940**s, the research was focused on individual microbial causes of illnesses which, as we know today, lead to disease only when the entire microbiome gets out of balance.

Up until **1980**, the probiotic strains were mainly isolated from nature and humans and the mechanisms of effects were studied.

The research around probiotics properly gained momentum only after the turn of the millennium. **In 2000, there were 176 publications on the subject, and by 2014, this number jumped to 1476.**

Clinical studies were carried out with hundreds of different probiotics and mixtures for different indications.

With such a piecemeal approach, it was very difficult - both for doctors and for patients/consumers - to find the right probiotics for individual diseases. It took time before it was determined that the effect was strain-specific in each case and the studies must always refer to a specific bacterial or fungal strain.

The more targeted the microbiome research was, the more precise the findings about probiotics and their interaction with the intestinal microbiome became. Today probiotics are clearly defined (see above).

In 2013, the World Gastroenterology Organization also confirmed that the effect of **probiotics depends on their strains and dosage**. For main strains and their effects, see point 6.

V. Microbiome

Since microbiome research has grown in importance, probiotics also have been taking more and more of the conversation, and the research has started to kick off again.

What is the microbiome?

The human microbiome includes an

> **"ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space"**
> (Lederberg *et al.*, 2001)

or as already defined in 1988:

> **"[...] the microbiome may be defined as a characteristic microbial community occupying a reasonably well defined habitat which has distinct physiochemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity."**
> (Whipps *et al.*, 1988).

Scientists have been intensively investigating this subject for almost two decades. For common people, bacteria, viruses and fungi are still rather unwelcome guests that are best kept at bay by using antibiotics, disinfectants, soaps and rinses.

> **"But in reality, these microorganisms enormously contribute to better health. Thus, it is high time that even non-scientists should be aware of the microbiome's usefulness."**
> Kristin Neumann, PhD

The number of microbes living with us (bacteria, viruses and fungi) are **1.3** times higher than the number of our body's own cells and they make up approximately **2 kg of our body weight**. The number of bacterial genes can even be **150 times more** than the number of our own human genes! These bacterial genes are important tools for us, which we do not possess ourselves, and we would not be able to survive without them.

> **"So far, we have seen this large bacterial population - that lives with us in a close symbiosis - as an enemy and did not realize that we were harming ourselves."**
> Kristin Neumann, PhD

These microorganisms help us with processing of nutrients, receiving signals from the body regarding our state of hunger or satiation, or to keep our immune system in check. They create vitamins, act as guards against harmful bacteria on our skin and in our intestines, and they help train and support our immune system.

V. Microbiome

How do we damage the microbiome?

Our **lifestyle** and our **hygiene behaviours** have a strong influence on the **diversity** of the microbiome, which starts at birth. More and more, babies are being delivered via a **Caesarean section**. In the course of this procedure, the baby is colonized with wrong germs that impede further colonisation with the right bacteria. The **mother's milk** makes an important contribution to the development of healthy microbiomes.

In addition, we tend to constantly **clean** - or even to **disinfect** - ourselves and everything around us.

Shower gels, shampoos, deodorants, toothpastes, mouth rinses, wound disinfectants and even cosmetics contain antimicrobial agents! Such products contain not only antimicrobial agents wilfully blended into them, but also **preservatives** to keep the product itself free of microbial contamination. In this case, less washing would make us cleaner!

But one of the greatest enemies of our microbiomes is the wonder weapon - antibiotics. It is clear that these drugs are very important in modern medicine and have saved many lives. They have been in use for almost a century, treated as if there were no side effects. But there are. One of the side effects is that it is not only the pathogenic microbes are destroyed, but the entire microbiome is also attacked!

> **An antibiotic cure is a cull of the microbiome - in and on the entire body!**

Systemically (perorally or intravenously) administered antibiotics are dispersed everywhere in the body and can even reach germs on the skin. Therefore, before taking an antibiotic, you should ask your treating doctor for a benefit/risk analysis. Of course, in some cases, antibiotics are simply necessary!

What is the effect of a damaged microbiome on my health?

Our way of life is shaped without taking into account the microbiome, a useful roommate in and on our bodies. Today, we more clearly see the side effects of our atrophied microbiome. Many of the diseases pervasive in society, such as **diabetes**, **asthma** and other **allergies**, **obesity** and **depression** are linked to an imbalance of our microbiome (also called dysbiosis).

In addition, there is a **higher susceptibility to disease-causing bacteria** (pathogens), because the immune system is weakened without the right microbes. The immune system can really work well, but only when it is paired with an intact microbiome.

VI. Probiotic strains and their effects

Probiotics are still controversially discussed. On the one hand, scientists attribute too many effects to probiotics, and on the other side, they claim that probiotics have no beneficial effects.

Both extremes have their justification, it depends on the details. Serious suppliers have packed the right strains in the right dosage into their products and also indicate the appropriate mode of action. Here is an excerpt about probiotic strains, with proven effects for each indication (complete list in the appendix)**.

Strain	Dose	Indication	Comment
Lactobacillus rhamnosus GG	10^{10} CFU/capsule twice daily	Antibtiotic associated diarrhoea (AAD)	Recommended by ESPGHAN
	≥10^{10} CFU/day (5-7 days)	Acute Gastroenteritis in Children	Recommended by ESPGHAN
	10^{10}–10^{11} CFU, twice daily	Prevention of nosocomial diarrhoea	
		Infections in children	Shown on children in day care centres
	10^{10}–10^{11} CFU, twice daily	Infantile colic prevention	
Saccharomyces boulardii CNCM I-745	5x10^{9} CFU/capsule or 250 mg twice daily	Antibtiotic associated diarrhoea	Recommended by ESPGHAN
	250-750 mg/day (5-7 days)	Acute Gastroenteritis in children	
	5x10^{9} CFU/capsule or 250 mg twice daily	Acute diarrhoea in adults	
L. reuteri DSM 17938	10^{8} daily up to 3 monaths old infants	Infantile colic prevention	
	10^{8} daily up to 21 days	Infantile colic management	reduced crying time (documented mainly in breastfed infants)
	10^{8} CFU/d for 4 weeks	Abdominal pain–related functional gastrointestinal disorders	Children

ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition

CFU: Colony Forming Units

VI. Probiotic strains and their effects

Strain	Dose	Indication	Comment
Yoghurt with *Lactobacillus casei* DN114, *L. bulgaricus*, and *Streptococcus thermophilus*	≥ 10^{10} CFU daily	Antibtiotic associated diarrhoea	
	10^{7}–10^{8} CFU twice daily	*Clostridium difficile*–associated diarrhoea	
Lactobacillus acidophilus CL1285 and *L. casei* LBC80R	5 × 10^{10} CFU daily and 4–10 × 10^{10} CFU daily	*Clostridium difficile*–associated diarrhoea	
Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	≥ 10^{10} CFU daily	Antibtiotic associated diarrhoea	
Mixture with *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii subsp. bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	900 billion bacteria daily	Treatment of IBD - Pouchitis	
Mixture with *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii subsp. bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1800 billion bacteria daily	Maintenance of clinical remission IBD – Pouchitis	

CFU: Colony Forming Units

VI. Probiotic strains and their effects

Strain	Dose	Indication
Escherichia coli Nissle 1917	5×10^{10} bacteria twice daily	Maintenance of clinical remission IBD – Ulcerative Colitis
Yoghurt with live cultures of *Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus*	At least 10^8 CFU of each strain per gram product	Lactose intolerance
Lactobacillus casei Shirota	6.5×10^9 in fermented milk, once daily	Reducing incidence of hard or lumpy stools

CFU: Colony Forming Units

Relevant studies are always carried out on a very specifically selected group of people. **Therefore, it is never clear whether generalised statements can be made about specific probiotics.** To choose the right probiotic, each patient should seek advice from their doctor. The research is now going the right direction, but very few of the questions about probiotic efficacy are clarified.

Influence by production of foodstuffs

Production of probiotic foods has a decisive influence on the effects of probiotics. In such foods, the probiotics should survive, and their probiotic properties should remain even after processing. A good example is ***Lactobacillus rhamnosus* GG** (abbr.: LGG), the most well-known and best-studied probiotic strain. LGG was primarily tested on babies and children. It demonstrates a very good healing effect in the case of malnourished children. This strain has a certain property that can be lost during cultivation and processing of LGG into a food product.

On its outer bacterial membrane, the LGG has appendages called pili, which enable the bacteria to attach to the intestinal wall for a while. During cultivation in the fermenter or even inoculation in yoghurt, the bacterium loses this property, because when the intestinal environment is missing, the bacterium does not need this property. Thus, the LGG strain cannot adhere to the intestine without this property nor remain there for a desirable time, and thus, it is unable to deliver the desired effect. **Therefore, the food product manufacturer should carry out appropriate quality checks and state their results.**

Furthermore, the probiotic should remain undamaged in the gastric passage and resistant against bile salts.

VI. Probiotic strains and their effects

How do probiotics work?

In principle, probiotics mostly ensure that the intestinal environment changes in such a way that a balanced microbiome can thrive in it. This is done either by release of different metabolites or by targeted release of anti-bacterial substances which eliminate pathogenic bacteria. In addition, probiotics push pathogenic microbes aside, impede their propagation, and clear the way for propagation of good bacteria.

How long do probiotics work?

> **Probiotics do not permanently colonize the intestine. They have their effect until they are excreted, but not longer. The effect lasts up to 3 weeks after the last dose.**

To achieve a lasting effect, you have to take the probiotic constantly.

VII. Safety of probiotics

Like the probiotic effect, safety of a probiotic very depends on its strain. Lactic acid bacteria have been used in food industry for more than 100 years and feature a high level of security. But other strains, e.g. clinical isolates, can cause health problems.

There are generally three theoretical risks which probiotics may cause:

- **Bacterial infections**
- **Toxic or metabolic effects on the digestive system**
- **Transfer of antibiotic resistance to the intestinal microbiome**

The EFSA (European Food Safety Authority) and the U.S. Food and Drug Administration (FDA) assess safety of probiotics and grants them the respective status of safety:

Qualified Presumption of Safety (QPS)
or
Generally recognized as safe (GRAS).

Doing so, scientific studies can be carried out on the probiotics, e.g. on their bioactive substances, activation of pro-carcinogens, mucin degradation, or transferable antibiotic resistance.

VIII. EFSA Issues

The EFSA refers to the European Food Safety Authority. In 2006 the EFSA decided that probiotics claim a health-related effect, and the potential buyer of the probiotic product automatically assumes that the product will be good for their health.

> **If a product has a Health Claim label, it must be proven by clinical studies.**

The EFSA steps in to evaluate these studies and recommends the product to the European Commission to approve the respective health-related statement.

Up to this day, the EFSA has still not considered even a single clinical probiotics study as sufficient for such a recommendation.

> **Therefore, there is still no product for which the EU Commission approved the usage of the word "probiotics" for marketing purposes.**

It is only in Italy that the government has managed to enforce the use of the word "probiotics" for products which meet the definition of the FAO/WHO.

This does not mean that probiotics have no health benefits. However, in the opinion of the EFSA the studies are still too imprecise or the study statements are too broadly phrased.

> **This strict approach of the EFSA is controversially discussed. Advertising statements from manufacturers are often simply too general. Also, in many cases, there is a lack of scientific evidence. Concrete and evidence-based statements are the right way to gain approval of using the "probiotics" term.**

IX. Prerequisites for a good probiotic

The basic requirement for a good probiotic is a precise declaration of its data.

- **The strain must be named exactly.**
- **The dose must be exactly specified for each strain.**
- **Its effectiveness must be shown in clinical trials for exactly the specified strain and the specified dosage (ask the manufacturer!).**
- **The probiotics need to be vital and survive in the stomach passage (stomach acid resistance).**

X. Author Kristin Neumann, PhD

Kristin Neumann, PhD in microbiology, has more than 12 years of experience in the field of microbiology research.

Since 2012, in collaboration with her very motivated team, she has developed new and selective-acting antibacterial agents, when intensively dealing with the microbiome topic.

In 2018, together with Tanja Walbrunn, a media designer and microbiome enthusiast, she founded a microbiome knowledge platform: **MyMicrobiome.info**.

The aim of this platform is to easy and understandably explain the importance of the microbiome issue to non-scientists and to contribute awareness of its health benefits.

Moreover, both power women developed the world's first and only certification for Microbiome friendly products.

XI. Recommended links

- https://isappscience.org/
- https://mailchi.mp/924419a2a520/clinical-guide-to-probiotic-products-newsletter-july-2019
- https://isappscience.org/is-probiotic-colonization-essential/
- https://www.nutraingredients.com/Article/2018/02/21/Probiotic-claims-on-the-horizon-so-long-as-new-EFSA-dossiers-keep-it-simple-say-regulatory-experts
- https://www.efsa.europa.eu/sites/default/files/event/190118-ax.pdf

XII. References

- Brüssow H: Probiotics and prebiotics in clinical tests: an update [version 1; peer review: 2 approved]F1000Research 2019, (F1000 Faculty Rev):1157
- McFarlund LV: From yaks to yogurt: the history, development, and current use of probiotics. Clin Infect Dis. 2015 May 15;60 Suppl 2:S85-90. doi: 10.1093/cid/civ054.
- Wilkins T, Sequoia J: Probiotics for Gastrointestinal Conditions: A Summary of the Evidence. f Am Fam Physician. 2017 Aug 1;96(3):170-178.
- * https://mailchi.mp/924419a2a520/clinical-guide-to-probiotic-products-newsletter-july-2019
- ** World Gastroenterology Organisation Global Guidelines: Probiotics and prebiotics (February 2017)

XIII. Annex

Excerpt from World Gastroenterology Organisation Global Guidelines: Probiotics and prebiotics

(February 2017)

Table 8 Evidence-based *adult* indications for probiotics, prebiotics, and synbiotics in gastroenterology. * Oxford Centre for Evidence-Based Medicine levels of evidence (see Table **7**)

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Diarrhea					
Treatment of acute diarrhea in adults	*Lactobacillus paracasei* B 21060 or *L. rhamnosus* GG	10^9 CFU, twice daily	3	[8]	–
	Saccharomyces boulardii CNCM I-745, strain of *S. cerevisiae*	$5x10^9$ CFU/capsule or 250 mg twice daily	2	[9,10]	–
Antibiotic-associated diarrhea	Yogurt with *Lactobacillus casei* DN114, *L. bulgaricus,* and *Streptococcus thermophilus*	≥ 10^{10} CFU daily	1	[11]	Prevention of AAD in various clinical settings (in-patients and outpatients)
	Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	≥ 10^{10} CFU daily	1	[11]	
	Lactobacillus rhamnosus GG	10^{10} CFU/capsule twice daily	1	[11]	
	Saccharomyces boulardii CNCM I-745	$5x10^9$ CFU/capsule or 250 mg twice daily	1	[11,12]	
	Lactobacillus reuteri DSM 17938	1×10^8 CFU twice daily	3	[13]	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* Bl-04	1.70^{10} CFU	2	[14]	
	Bifidobacterium bifidum W23, *B. lactis* W18, *B. longum* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37 and W55, *L. paracasei* W72, *L. plantarum* W62, *L. rhamnosus* W71, and *L. salivarius* W24	10^9 CFU/g (5 g twice daily)	2	[15]	–
Prevention of *Clostridium difficile*–associated diarrhea (or prevention of recurrence)	*Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R	5×10^{10} CFU daily and $4–10 \times 10^{10}$ CFU daily	2	[16]	–
	Yogurt with *Lactobacillus casei* DN114 and *L. bulgaricus* and *Streptococcus thermophilus*	$10^7–10^8$ CFU twice daily	2	[17]	–

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Saccharomyces boulardii CNCM I-745	$5x10^9$ CFU/capsule or 250 mg twice daily	3	[17]	–
	Lactobacillus rhamnosus HN001 + *L. acidophilus* NCFM	10^9 CFU once daily	3	[18]	Reduced fecal counts of *Clostridium difficile* in healthy elderly patients without diarrhea
	Lactobacillus acidophilus + *Bifidobacterium bifidum* (Cultech strains)	2×10^{10} CFU, once daily	3	[19]	–
	Oligofructose	4 g, three times daily	3	[20]	–
***Helicobacter pylori* (HP)**					
Coadjuvant therapy for HP eradication	*Lactobacillus rhamnosus* GG	6×10^9 twice daily	2	[7]	Reduction in therapy-related side effects in first line therapy
	Bifidobacterium animalis subsp. *lactis* (DSM15954), *Lactobacillus rhamnosus* GG	10^8–10^{10} living bacteria twice daily	2	[21]	Reduction in therapy-related side effects
	Lactobacillus reuteri DSM 17938	1×10^8, CFU three times daily	2	[22]	Reduction in therapy-related side effects in levofloxacin second-line therapy
	Mixture of *Lactobacillus acidophilus* and *L. bulgaricus* and *Bifidobacterium bifidum* and *Streptococcus thermophilus* and galacto-oligosaccharides	$5 \times 10^8 + 1 \times 10^9$, live cells twice daily	2	[23]	Improves treatment compliance in sequential therapy
	Lactobacillus acidophilus, Streptococcus faecalis, Bacillus subtilis	5×10^6, 2.5×10^6, 5×10^3	3	[24]	Improves eradication rates in first-line therapy
	Saccharomyces boulardii CNCM I-745	$5x10^9$ CFU/capsule or 250 mg twice daily	1	[7]	Reduction in therapy-related side effects
	Kefir	250 mL twice daily	3	[25]	

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Bacillus clausii (Enterogermina strains)	2×10^9 spores, three times daily	2	[26]	
	Lactobacillus reuteri DSM 17938 and *L. reuteri* ATCC 6475,	1×10^8 CFU of each strain, twice daily	2	[27,28]	–
Liver disease					
Hepatic encephalopathy	Nonabsorbable disaccharides (lactulose)	45–90 g/daily	1	[29]	–
	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1×10^8 CFU three times daily	2	[30]	Primary prophylaxis of HE
	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1×10^8 CFU three times daily	2	[31,32]	Secondary prophylaxis of HE
	Yogurt with *Streptococcus thermophilus, Lactobacillus bulgaricus, L. acidophilus,* bifidobacteria, and *L. casei*	12 ounces daily	2	[33]	Improvement in minimal hepatic encephalopathy
NAFLD	Yogurt (with *Lactobacillus bulgaricus* and *Streptococcus thermophilus*) enriched with *L. acidophilus* La5 and *Bifidobacterium lactis* Bb12	300 g daily	3	[34]	Improvement in aminotransferases
	Mixture of *Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, B. longum,* and *L. bulgaricus* + fructo-oligosaccharides	At least 10^7 CFU twice daily	3	[35,36]	Improvement in aminotransferases, along with improve HOMA-IR and transient elastography

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
NASH	*Lactobacillus bulgaricus* and *Streptococcus thermophilus*	A tablet with 500 million, once daily	3	[37]	Improvement in aminotransferases
	Bifidobacterium longum W11 + FOS	5,000 million live bacteria once daily	2	[38]	Improvement in aminotransferases and NASH histological activity score
IBS					
	Bifidobacterium bifidum MIMBb75	1×10^9 CFU once daily	3	[39]	Improvement in global IBS symptoms and QOL
	Lactobacillus plantarum 299v (DSM 9843)	10 billion CFU once daily	2	[40,41]	Improvement in severity of abdominal pain
	Escherichia coli DSM17252	10^7 CFU three times daily	2	[41]	–
	Lactobacillus rhamnosus NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175, and *Enterococcus faecium* NCIMB 30176.	10 billion bacteria	2	[42]	Improvement in IBS score, mainly in pain and bowel habit score
	Bacillus coagulans and fructo-oligosaccharides	15×10^7, three times daily	2	[43]	Decrease pain, improve constipation
	Lactobacillus animalis subsp. *lactis* BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27, *Streptococcus thermophilus* STY-31	4 billion CFU, twice daily	3	[44]	Improvement in abdominal pain and bloating
	Saccharomyces boulardii CNCM I-745	$5x10^9$ CFU/capsule or 250 mg twice daily	2	[45]	Improvement in IBS QOL score
	Bifidobacterium infantis 35624	10^8 CFU, once daily	2	[46,47]	Improvement in subjects global assessment of IBS symptoms
	Bifidobacterium animalis DN-173 010 in fermented milk (with *Streptococcus thermophilus* and *Lactobacillus bulgaricus*)	10^{10} CFU, twice daily	2	[48,49]	Improvement in HRQOL in constipation-predominant IBS

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus acidophilus SDC 2012, 2013	10^{10} CFU, once daily	3	[41,50]	–
	Lactobacillus rhamnosus GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* subsp. *shermanii* JS DSM 7067, *Bifidobacterium animalis* subsp. *lactis* Bb12 DSM 15954	10^{10} CFU, once daily	2	[41,51]	–
	Short-chain fructo-oligosaccharides	5 g/daily	3	[52]	–
	Galacto-oligosaccharides	3.5 g/daily	2	[53]	–
	Bacillus coagulans GBI-30, 6086	2×10^9 CFU, once daily	3	[54]	–
	Pediococcus acidilactici CECT 7483, *Lactobacillus plantarum* CECT 7484, *L. plantarum* CECT 7485	$3–6 \times 10^9$ CFUs/capsule, once daily	3	[55]	–
Functional constipation					
	Bifidobacterium bifidum (KCTC 12199BP), *B. lactis* (KCTC 11904BP), *B. longum* (KCTC 12200BP), *Lactobacillus acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), and *Streptococcus thermophilus* (KCTC 11870BP)	2.5×10^8 viable cells once daily	3	[56]	Improvement in elderly, in nursing-home population
	Lactobacillus reuteri DSM 17938	1×10^8, CFU twice daily	3	[57]	Improvement in bowel movement frequency per week
	Lactulose	20–40 g/d	2	[58]	–
	Oligofructose	20 g/d	3	[59]	–
	Fructo-oligosaccharide (FOS) and *Lactobacillus paracasei* (Lpc-37), *L. rhamnosus* (HN001), *L. acidophilus* (NCFM) and *Bifidobacterium lactis* (HN019)	6 g (FOS) + 10^8–10^9 CFU once daily	3	[60]	–
Uncomplicated symptomatic diverticular disease					
	Lactobacillus casei subsp. DG	24 billion viable lyophilized bacteria daily	2	[61]	Improvement in symptoms in uncomplicated diverticular disease

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus paracasei B21060	5×10^9 CFU daily	3	[62]	Improvement in symptoms in uncomplicated diverticular disease
Postoperative sepsis in elective gastrointestinal surgery patients					
	Lactobacillus acidophilus, L. plantarum, and *Bifidobacterium longum* 88	2.6×10^{14} CFU daily	1	[63]	–
Small-bowel injury from NSAIDs					
	Lactobacillus casei strain Shirota	45×10^8 to 63×10^9 CFU, once daily	3	[64]	Decreased the incidence and severity of low-dose aspirin-associated small-bowel injury
IBD—pouchitis					
Treatment of active pouchitis	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	900 billion bacteria daily	2	[65]	–
Maintenance of clinical remission	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1800 billion bacteria daily	1	[66]	–
IBD—ulcerative colitis					

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Inducing remission	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1800 billion bacteria twice daily	3	[67]	–
Maintenance of clinical remission	*Escherichia coli* Nissle 1917	5×10^{10} viable bacteria twice daily	2	[68,69]	–
Lactose maldigestion—reducing associated symptoms					
	Yogurt with live cultures of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*	At least 10^8 CFU of each strain per gram of product	1	[70]	–
Healthy population—reducing incidence of hard or lumpy stools					
	Lactobacillus casei strain Shirota	6.5×10^9 in fermented milk, once daily	3	[71]	–

AAD, antibiotic-associated diarrhea; CFU, colony-forming unit(s); HE, hepatic encephalopathy; HRQOL, Health-Related Quality of Life (score); IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.

Table 9 Evidence-based *pediatric* indications for probiotics, prebiotics, and synbiotics in gastroenterology. * Oxford Centre for Evidence-Based Medicine levels of evidence (see Table **7**)

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Treatment of acute gastroenteritis	LGG	≥ 10^{10} CFU/day (typically 5–7 days)	1	[72,73]	ESPGHAN/ESPID recommendations 2014; ESPGHAN Working Group on Probiotics. Meta-analysis of RCTs
	Saccharomyces boulardii CNCM I-745	250–750 mg/day (typically 5–7 days)	1	[72,74]	
	Lactobacillus reuteri DSM 17938	10^8 to 4 × 10^8 CFU (typically 5–7 days)	2	[72,73,75,76]	
	Escherichia coli Nissle 1917		3	[72]	ESPGHAN/ESPID: insufficient evidence to make a recommendation (methodological issues)
	Lactobacillus acidophilus	10 × 10^9 CFU	3	[72,77]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (no strain specification)
	Lactobacillus acidophilus and *Bifidobacterium bifidum*	3 × 10^9 CFU, for 5 days	3	[72,78]	
	Lactobacillus acidophilus and *Bifidobacterium infantis*	3 × 10^9 CFU of each organism for 4 days	3	[72,79]	
	Lactobacillus acidophilus rhamnosus 573L/1, 573L/2, 573L/3	1.2 × 10^{10} CFU twice daily, for 5 days)—effect only in RV diarrhea	2	[72,80]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (only one RCT available)
	Lactobacillus helveticus R0052 and *L. rhamnosus* R0011		2	[72,81]	
	Lactobacillus delbrueckii var. *bulgaricus, L. acidophilus, Streptococcus thermophilus, Bifidobacterium bifidum* (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500)	10^9 CFU, 10^9 CFU, 10^9 CFU, and 5 × 10^8 CFU	2	[72,82]	

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Bacillus mesentericus and *Clostridium butyricum* and *Enterococcus faecalis*	1.1 × 10^7 CFU) & *Clostridium butyricum* (2.0 × 10^7 CFU) and *Enterococcus faecalis* (3.17 × 10^8 CFU)	3	[72,83]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (only one RCT available and no strain identification))
	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.		3	[72,84]	
	Lactobacillus acidophilus & *L. rhamnosus* & *Bifidobacterium longum* & *Saccharomyces boulardii* CNCM I-745		3	[72,85]	
Prevention of antibiotic-associated diarrhea	LGG	1–2 × 10^{10} CFU	1	[86,87]	ESPGHAN Working Group on Probiotics
	Saccharomyces boulardii	250–500 mg	1	[12]	
Prevention of nosocomial diarrhea	LGG	10^{10}–10^{11} CFU, twice daily	1	[12]	Meta-analysis of RCT
	Bifidobacterium bifidum and *Streptococcus thermophilus*		2	[88]	–
Infections in children attending day-care centers	LGG		1	[89–91]	Prevention of AAD in hospitalized patients
	Lactobacillus reuteri DSM 17938	1 × 10^8 CFU/day for 3 months	2	[92,93]	

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus casei DN-114 001 in fermented milk	10^{10} CFU, once daily	2	[94–96]	–
	Lactobacillus casei Shirota in fermented milk	10^{10} CFU, once daily	2	[97]	–
Eczema (prevention)	(Probiotics) There is no clear indication yet regarding which probiotic(s) to use.			[98,99]	WAO suggests the use of probiotics in high-risk populations to reduce the risk of eczema
Necrotizing enterocolitis (prevention)	(Probiotics) No clear indications from scientific societies regarding which probiotic strain(s) should be recommended. The following strains are found NOT to be effective: *Saccharomyces boulardii* CNCM I-745, *Bifidobacterium breve* BBG-001, Bb12			[100,101]	Reduced risk of NEC and mortality in infants with birth weight < 1500 g
	Lactobacillus reuteri DSM 17938		2	[102]	–
H. pylori infection	*Saccharomyces boulardii* CNCM I-745	500 mg (in two doses, for 2–4 weeks)	2	[103]	Reduced risk of side effects and increased eradication rate
	Lactobacillus casei DN-114 001 in fermented milk	10^{10} CFU daily, for 14 days	2	[104]	–
Infantile colic—management	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, for 21 days	1	[105–110]	Reduced crying time (documented mainly in breastfed infants). Meta-analysis of RCTs
Infantile colic—prevention	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, up to 3 months of age	1	[111]	–
	LGG	10^{10}–10^{11} CFU, twice daily	1	[112]	Meta-analysis of RCTs

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Abdominal pain–related functional gastrointestinal disorders	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	1 sachet (once per day for children 4–11 years of age; twice per day for those 12–18 years old)	3	[113]	–
	Lactobacillus reuteri DSM 17938	10^8 CFU/d for 4 weeks	1	[114,115]	–
Induction of remission in ulcerative colitis	*Escherichia coli* Nissle 1917		2	[116,117]	ESPGHAN/ECCO: Limited evidence suggests that probiotics added to standard therapy may provide modest benefit
	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius*.	4 to 9 × 10^{11} CFU, twice daily	2	[118,119]	–

AAD, antibiotic-associated diarrhea; CFU, colony-forming unit(s) ECCO, European Crohn's and Colitis Organization; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; ESPID, European Society for Paediatric Infectious Diseases; LGG, *Lactobacillus rhamnosus* GG ; NEC, necrotizing enterocolitis; RCT, randomized controlled trial.