

Probiotics: growing science and need for proper consumer communication on probiotic food supplements

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1. Introduction and background

Scientific research on probiotics continues to grow worldwide. In 2020 alone, over 4,300 publications were devoted to probiotics. In particular, a number of recent meta-analyses and systematic reviews show the increasing consensus on the role that probiotics can play in certain fields of health. An example is the consensus in the scientific community that the consumption of probiotic micro-organisms favours the maintenance of a healthy intestinal microbiota, helping protect against the many factors that can push the flora towards dysbiosis.

However, it is not always easy for people to find appropriate information about probiotics on foods. The EU's 2006 Nutrition & Health Claims Regulation forbids to use the term 'probiotic' for food products (see Annex I). It also requests that all probiotic related health benefits must be authorised by the European Commission after an assessment by the European Food Safety Authority (EFSA). So far, in spite of the strong literature supporting the general health benefits of probiotics (see Annex II), EFSA has rejected all submitted health claims for probiotics, with the exception of the effect of the standard yoghurt cultures on lactose digestion.

In contrast, as concerns the use of the term 'probiotic' for the designation of (good or beneficial) bacteria & yeasts in health recommendations and communications, scientific bodies and official authorities frequently do refer to 'probiotics'. For example, the European Society for Paediatric Gastroenterology Hepatology & Nutrition (ESPGHAN) strongly recommends three probiotics for the management of children with acute gastroenteritis.¹ In the UK, the National Health Service (NHS) explains what probiotics are on their website and indicates that probiotics may be helpful in some cases.²

In addition, in other consumer goods sectors, such as cosmetics and pet foods, the term 'probiotic' is widely used and is therefore familiar to people. Consumer research carried out by FSE members illustrates that the term 'probiotic', which was commonly used in the past, is well known by consumers. Its use on food supplements would not bring a new or stronger message than the knowledge consumers already have. It would however facilitate consumer identification of the products.

Therefore, while European consumers often hear about 'probiotics', they are not able to find foods and food supplements with that characteristic in the market. The prohibition of indicating the term 'probiotic' on the label makes it difficult for consumers in most EU Member States to identify such products on-shelf. Consumers would need certain knowledge to find the product they are seeking.

A consumer survey in Ireland found that 79% of people want to be educated about digestive health – and most of them get their information from the internet, including social media.³

How the benefits of probiotics can be communicated and how products can be identified are crucial to help consumers take care of their own health. This current regulatory situation on probiotic products does not serve the best interests of consumers, and this has consequences for public health. FSE believes that it is time to consider revisiting the current guidance on the use of the word 'probiotic' and to review how probiotics are assessed in relation to health claims.

1 Szajewska, H, et al. ESPGHAN J. Pediatr. Gastroenterol. Nutr. 2014, 58(4): 531–539.

2 NHS. <https://www.nhs.uk/conditions/probiotics/>

3 The SCOPE Gut Education Index 2019.

<https://docplayer.net/138544027-Understanding-gut-power-and-its-impact-on-our-insides-the-scope-gut-education-index-2019.html>

2. Nomenclature and definition

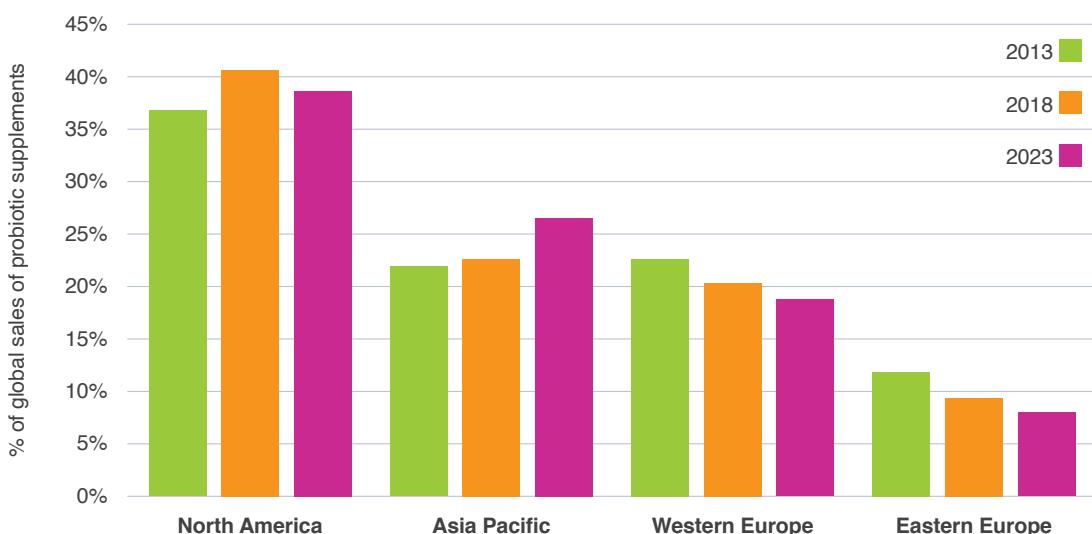
Probiotics are micro-organisms that are typically ingested through foods, beverages and supplements in order to deliver health benefits to the consumer. However, in the EU, the word 'probiotic' cannot be used when marketing a food or food supplement because it is considered a general health claim that may be used only in the presence of an authorised health claim for a specific microorganism (see note in Annex I).

This has been the case since 2007, when the European Commission published guidelines on how to interpret certain provisions of the 2006 Nutrition & Health Claims Regulation.⁴ This non-binding agreement, which most EU Member States currently enforce, prohibits the use of the term 'probiotic' on product labels, if this has not been specifically authorised as a health claim or used in association with an authorised health claim for a specific microorganism. Subsequently, in 2011, EFSA published guidance on the scientific requirements for health claims related to gut and immune function (updated again in 2016).⁵

The 2007 guidelines state that the scientific name of a micro-organism is generally acceptable for use in communications, but this may not be well understood by consumers. The most common strains of bacteria used as probiotics are lactic acid-producing micro-organisms belonging to the genus Lactobacilli, Lactococci, Enterococci, Bifidobacteria, Streptococci and the yeast *Saccharomyces boulardii*. However, there is limited public understanding of such technical terminology.

This situation has contributed to a decline in the use of probiotic products in the EU, relative to other regions in the world where the use of the term in marketing is permitted.

Probiotic supplements % sales by region 2013 / 2018 / 2023



Source: Euromonitor

4 European Commission. Guidance on the implementation of regulation n° 1924/2006 on nutrition and health claims made on foods conclusions of the standing committee on the food chain and animal health. 14 December 2007.
https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition_claim_reg-2006-124_guidance_en.pdf

5 EFSA Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. EFSA Journal 2016;14(1):4369, 23 pp. doi:10.2903/j.efsa.2016.4369
<https://efsajournal.efsa.europa.eu/doi/10.2903/j.efsa.2016.4369>

This is in spite of growing awareness that the gut microbiome is crucial for the development of the immune function and a reduction of the risk of disease. The EU itself has expressed interest in this field of research, as exemplified by its decision to award a €9 million grant to the MyNewGut 7th Framework Programme and support the International Human Microbiome Coordination & Support Action (IHMCSA).^{6,7}

Criteria for micro-organisms to be considered as probiotics and to be covered by the generic term probiotic have been laid down in a consensus document by the International Scientific Association for Probiotics & Prebiotics.⁸ This states that, when a product indicates it contains probiotics:

- The micro-organism in question must have been scientifically shown to be a member of a safe species, which is supported by sufficient evidence of a general beneficial effect in humans OR a safe microbe with a property (e.g. a structure, activity or end product) for which there is sufficient evidence for a general beneficial effect in humans.
- Proof of viability at the appropriate level used in supporting human studies must be available.

Consumers – also those prescribed antibiotics – could benefit greatly from food supplements that contain probiotics. However, for this potential to be realised, it is also essential for people to be given the tools they need to correctly understand and interpret the advice provided to them by healthcare professionals and health authorities. As such, permitting manufacturers to use declarations such as 'contains probiotics' would be a significant and positive step towards improving public health.

6 <https://cordis.europa.eu/project/id/613979?rcn=177501>

7 https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/ec_rtd_new-health-h2020-projects.pdf

8 Hill C. et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014 Aug; 11(8):506-14
<https://www.nature.com/articles/nrgastro.2014.66.pdf>

3. Health effects and claims

There is a multitude of scientific studies available demonstrating the health effects of probiotics, many of which have been published since the introduction of the 2006 Nutrition & Health Claims Regulation.

The most recent comprehensive overview of the value of probiotics for health and disease is to be found in the 2017 World Gastroenterology Organisation (WGO) Global Guidelines on Pre- and Probiotics.⁹ This identifies the effects of probiotics that are supported by clinical research and meta-analyses, and are therefore suitable as a basis for science-based recommendations. The effects, marked with * cover both effects considered by EFSA as beneficial and/or conditions for which study results can be used in support of a health benefit/claim. Other effects are considered therapeutic (and thus not appropriate for food supplements):

- Strong evidence of efficacy in adults or children with antibiotic-associated diarrhea *
- Reduction of the risk of developing *C. difficile*-associated diarrhea with antibiotics *
- Improvement of the immune response – shown in studies aimed at the prevention of acute infectious disease (nosocomial diarrhea in children, influenza episodes in winter) and testing antibody responses to vaccines *
- Reduction of the severity and duration of acute infectious diarrhea in children
- Prevention and treatment of radiation-induced diarrhea
- Reduction of abdominal bloating and flatulence in inflammatory bowel disease
- Reduction of the risk of necrotizing enterocolitis in preterm neonates
- Improvement of biomarkers associated with colorectal cancer
- Mitigation of steatohepatitis in adults and children
- Effectiveness in infant colic

Several of these health effects address diseases or medical conditions. Communication on therapeutic effects is not permitted and would not be appropriate for probiotic food supplements. Nevertheless, the WGO guidebook reflects increased understanding of how probiotics are capable of mitigating mechanisms such as gut barrier and inflammation, which underlie a plethora of disease conditions. These health effects are supported by a significant number of reviews and meta-analyses published in the past two years (see Annex II).

⁹ The WGO is the global federation of gastroenterological societies and is comprised of over 100 Member Societies and 4 Regional Associations representing more than 50,000 gastroenterologists, hepatologists, GI surgeons and other healthcare professionals worldwide.
<https://www.worldgastroenterology.org>

Under the Nutrition & Health Claims Regulation, EFSA has already identified and accepted outcome parameters for the substantiation of health benefits that are pertinent to the effects itemised in the WGO guidelines. For example:

- EFSA considers demonstrating a reduction in *C. difficile* toxins to be an acceptable risk reduction factor.
- It considers human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms) in people without an infection at baseline to be acceptable evidence for the scientific substantiation of health claims related to defence against pathogens.
- Irritable bowel syndrome-related outcomes are acceptable outcome parameters for people in good health.
- Measuring antibody response to vaccines is an acceptable outcome.

However, in its guidance on the scientific requirements for health claims related to gut and immune function, EFSA states that outcome variables which do not refer to a benefit for specific functions of the body cannot be used for the scientific substantiation of a health claim. This stipulation covers changes in the following:

- The composition of the gut microbiota
- Immune markers and markers of inflammation
- Microbial metabolites (e.g. short-chain fatty acid production)
- The structure of the intestinal epithelium

As a result, although EFSA has identified physiological and clinical outcomes as possibilities to demonstrate such effects, all applications for health claims related to probiotics lodged in the past 14 years have received negative opinions.¹⁰ This is despite a strong consensus in the scientific literature that probiotics survive in the gut, modulate the immune response and produce metabolites with expected favourable effects in the body. But since these effects have not been shown to be immediately associated with a measurable health outcome, they have not been accepted by EFSA.

Furthermore, with regards to the 2007 Commission guidance, the EFSA guidelines on the scientific requirements for health claims related to gut and immune function means that, in effect, there are no circumstances in which the term 'probiotic' can be authorised as a health claim, since it is not sufficiently precise.

¹⁰ Only the effect on lactose digestion of traditional yoghurt cultures has been authorised as a health claim.

The inherent contradictions between the Nutrition & Health Claims Regulation and subsequent guidelines indicate a need to review the regulation and how health claims for probiotics are assessed.

This is in contrast to the global regulatory environment for the use and communications of probiotics. In other jurisdictions, such as the US, Japan, Canada, Switzerland, Korea and Singapore, not only the term 'probiotic' is allowed (under certain conditions), but also other non-strain specific health benefits can be communicated to consumers. Australia defines a probiotic as a product containing live bacteria that is taken orally to restore the body's beneficial bacteria.¹¹

As the Expert Consensus Document on the scope and appropriate use of the term probiotic by the International Scientific Association for Probiotics and Prebiotics confirms:

"Thus, Canada and Italy consider the general benefit of supporting a healthy gut microbiota to be a core benefit of probiotics. The consensus panel agrees with this approach, while acknowledging that the current state of science does not allow the clear definition of a healthy gut microbiota based on microbial composition. Nevertheless, the general benefit of probiotics on gut microbiota derives from creating a more favourable gut environment, through mechanisms shared by most probiotics".⁸

The effect on a healthy gut microbiota should therefore be a sufficient reason in itself to enable consumers to identify relevant products by appropriately allowing the use of the term 'probiotic'.

In addition, how probiotics can contribution to a broader public health in various areas is addressed in the next section.

¹¹ <https://www.tga.gov.au/book-page/advertising-interface-products>

4. A role for probiotics in public health

By virtue of their benefits, probiotic products can contribute significantly to the health of the population and, therefore, generate savings for the healthcare systems.

A study in France assessed the public health and budget impact of the use of probiotics on common respiratory tract infections (CRTI). It found that generalised probiotic use could eliminate the equivalent of 2.4 million days of CRTI infection, 581,000 days of sick leave and 291,000 courses of antibiotics – generating healthcare savings of between €14.6 million and €37.7 million a year.¹² Probiotics are largely consumed through dairy products and food supplements, which are low cost, widely available, easy to ingest, well tolerated and safe. As such, delivering their benefits to the wider population is easy and relatively inexpensive.

An interesting example is the practical guide that is published in The Netherlands.¹³ It informs healthcare professionals on the availability of probiotic products with a proven efficacy in cases of antibiotic-associated diarrhea.

In this light, it is encouraging that a recent international survey on health professionals' knowledge of probiotics involving 1066 health professionals from 30 countries (of which 90% of respondents from European countries) confirms the level of knowledge and awareness about the beneficial role of probiotics in health and disease.¹⁴ In fact, 90.2% of health professionals identified that probiotics have beneficial effects if taken during antibiotic therapy; 83.5% for diarrhea; 70.6% for constipation; 63.3% before travelling abroad; and 60.4% for treating allergies. 79% of health professionals involved in this study said they have advised the use of probiotics.

While most of the respondents evaluated their knowledge of probiotics as either excellent (8.9%), good (36.2%) or medium (36.4%), the fact that 57.5% wanted to learn more about probiotics is indicative of a lack of information, possibly linked to the regulatory situation on probiotics.

This is important given the important role of health professionals in giving informed and objective advice on probiotics to consumers, as the current EU legislation on nutrition and health claims prevents manufacturers from explaining their probiotic products to the consumers.

For this reason, regulators in Italy have adopted a different position to the EU's. Provided that manufacturers can demonstrate for their probiotic a history of use, safety, and activity in the intestines in such a quantity as to be able to multiply there, the Italian authorities permit the use of the term 'probiotic' and allow products containing probiotics to be marketed as promoting the balance of the intestinal flora (*Favorisce l'equilibrio della flora intestinale*).¹⁵ According to EFSA's guidelines, this cannot be considered as a beneficial health effect per se. But it is nevertheless useful information that could help consumers to identify the right products if they are advised to take a probiotic by a health professional or wish to follow guidelines issued by medical bodies and official authorities to do so.

12 Lenoir-Wijnkoop I, Gerlier L, Bresson J.L., Le Pen C, Berdeaux G. Public Health and Budget Impact of Probiotics on Common Respiratory Tract Infections: A Modelling Study. PLOS ONE DOI:10.1371/journal.pone.0122765 April 10, 2015

13 Agamennone V et al. A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. BMC Gastroenterology volume 18, Article number: 103 (2018)

14 Figan S. et al. Health Professionals' Knowledge of Probiotics: An International Survey. Int J Environ Res Public Health. 2019 Sep; 16(17): 3128.

15 Ministero della Salute. Guidelines for probiotics and prebiotics. December 2005, revised March 2018. http://www.salute.gov.it/imgs/C_17_pubblicazioni_1016_ulterioriallegati_ulterioreallegato_0_alleg.pdf

Recently, Spain has accepted the use of the term 'probiotic' on food products also.¹⁶ Also in Czech Republic the use of the term 'probiotic' is allowed.¹⁷

With this in mind, FSE believes that consumers across the whole of the EU would benefit greatly from the use of clearer signposting of probiotic products – and permitting manufacturers to state that their products contain probiotics would be a straightforward and effective way to achieve this.

Furthermore, FSE also suggests that the criteria of the EU Nutrition & Health Claims Regulation should be reviewed to take account of new knowledge and methodologies in relation to probiotics, in order that their specific health effects can be approved and communicated with appropriate language to consumers for the benefit of public health.

¹⁶ Ministerio De Consumo. Agencia Española de Seguridad Alimentaria y Nutrición. https://www.aesan.gob.es/AECOSAN/web/seguridad_alimentaria/subdetalle/probioticos.htm?idU=1&utm_source=newsletter_1712&utm_medium=email&utm_campaign=importante-probioticos-etiquetado

¹⁷ Národní doporučení přístupu k některým označením potravin zejména ve vztahu k nařízení Evropského parlamentu a Rady (ES) č. 1924/2006 ze dne 20. prosince 2006 o výživových a zdravotních tvrzeních při označování potravin. Ze dne 21. 11. 2013 http://eagri.cz/public/web/file/661593/Narodni_doporupecni_pristupu_k_nekterym_oznacenim_potravin_zejmena_ve_vztahu_k_narizeni_ES_c._19242006.pdf

Annex I: Note on the use of the term 'probiotic'

The current practice that most, but not all, EU Member State authorities do not allow the use of the term 'probiotic' on food supplement labels does not stem from the 2006 Nutrition & Health Claims Regulation itself, but from non-legally binding interpretative guidelines published in 2007.¹⁸ This was long before the first health claims were assessed and the requirements became clear (EFSA only published detailed guidelines in 2011). At the time, EU Member States could not know that EFSA would not accept changes in the microflora or in immune parameters as subjects for health claims and that an application for a health claim for probiotics in general would never be possible.

In fact, the Nutrition & Health Claims Regulation permits statements to the effect that a food simply 'contains' a certain substance with a nutritional or physiological effect. The guidelines, however, further restrict this possibility by requiring additionally that when the 'contains' statement refers to a substance, the name of which refers to a function in the body (e.g. antioxidant and pre- and probiotic) it can no longer be a nutrition claim but should be authorised as a health claim.

The validity of the interpretation that the statement 'contains probiotics' is expressing a health benefit is highly questionable for two reasons:

- Unlike 'antioxidant', which refers to a clear and measurable effect, the term 'probiotic' does not refer to an effect, but rather to a group of micro-organism that share a common property: they are live or viable in the product and when ingested arrive in the gastro-intestinal tract. They carry the potential to change the composition of the microflora. The term 'probiotic' therefore does not characterise a health claim. There may be specific health benefits but these are not expressed by the term 'probiotic' as such.
- On food supplements it is a legal obligation under article 6.3.a to indicate in the labelling "the names of the categories of nutrients or substances that characterise the product; or an indication of the nature of those nutrients or substances". 'Probiotic' is the generally recognised term that covers micro-organisms added to food supplements and has been since long before the Nutrition & Health Claims Regulation was adopted. In this respect it is the same as stating 'contains vitamins and minerals', 'contains fibre' or even 'contains milk'. In all of these cases there may be beneficial effects, but this is not expressed by the simple indication of the nutrients or other substances the product contains. It cannot therefore be inferred that the simple mentioning of the category of substances is a health claim by itself.

In this respect, the term 'probiotic' is unspecific and does not infer or refer to a health benefit. In this context it is worth noting as well, that it does not include a reference to health (health condition or benefit), as do the terms 'biscotto salute', 'cough drops', 'tonic', that have been accepted as generic descriptors.¹⁹

¹⁸ European Commission. Guidance on the implementation of regulation n° 1924/2006 on nutrition and health claims made on foods conclusions of the standing committee on the food chain and animal health. 14 December 2007. https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition_claim_reg-2006-124_guidance_en.pdf

¹⁹ Regulation (EU) 2019/343

Annex II: Recent meta-analyses and systematic reviews supporting the health benefits of probiotics

Paper: Miller E et al. Short-term probiotic supplementation enhances cellular immune function in healthy elderly: systematic review and meta-analysis of controlled studies. *Nutrition* 64 (2019) p. 1-8

Summary: Review and meta-analysis to evaluate the effect of probiotic supplementation on cellular innate immune activity in healthy elderly people (since immune function declines with advancing age).

Conclusion: Short-term probiotic supplementation enhances cellular immune function in healthy elderly adults. The clinical benefit of these immune changes is unclear.

Paper: Hajavi J et al. The immunomodulatory role of probiotics in allergy therapy. *J Cell Physiol*. 2019;234:2386–2398

Summary: Review of published literature exploring the benefits of probiotics for allergies.

Conclusion: Many studies have confirmed the modulatory effect of probiotics for regulating inflammatory allergic responses and, therefore, probiotics could be used to treat allergic diseases.

Paper: Yu Y et al. Changing our microbiome: Probiotics in dermatology. *Br J Dermatol*. 2019 May 3. doi: 10.1111/bjd.18088

Summary: Review of published literature evaluating whether the clinical data support the use of oral and topical probiotics for certain dermatological diseases.

Conclusion: The microbiome plays an important role in dermatology and serves as a potential target for treatment. Oral probiotics appear to be effective for the treatment of certain inflammatory skin diseases and demonstrate a promising role in wound healing and skin cancer. However, more studies are needed to confirm these results.

Paper: Goldenberg G et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea (Review). Cochrane database of systematic reviews. 2019, Issue 4. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub5

Summary: Systematic review of published literature to assess the efficacy of probiotics (any specified strain or dose) used for the prevention of antibiotic-associated diarrhea in children.

Conclusion: The overall evidence suggests a moderate protective effect of probiotics for preventing antibiotic-associated diarrhea.

Paper: Setbo E et al. Utility of probiotics for maintenance or improvement of health status in older people – a scoping review. J Nutr Health Aging. 2019;23(4):364-372

Summary: Systematic review to evaluate the available evidence on probiotic use in older adults from human studies, addressing age-related conditions including gut dysmotility, osteoporosis, common infectious diseases and cognitive impairment.

Conclusion: Probiotics used in the prevention of common infectious disease when provided long term (>5 months) reduced the duration and frequency of symptoms. In osteoporosis treatment the benefit in calcium absorption and osteogenesis has translated into clinically significant results. Earlier recovery of upper limb fracture shows this effect can result in improved functional status. Probiotics may have a role in supportive care of people with Alzheimer's dementia.

Paper: Miller L et al. Probiotic supplementation decreases intestinal transit time: Metaanalysis of randomized controlled trials. World J Gastroenterol 2013 August 7; 19(29): 4718-4725

Summary: A systematic review of randomized controlled trials (RCTs) of probiotic supplementation measuring intestinal transit time in adults

Conclusion: Overall, short-term probiotic supplementation decreases intestinal transit time with consistently greater treatment effects identified in constipated or older adults and with certain probiotic strains.

Paper: Tidari T et al. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World J Gastroenterol* 2015 March 14; 21(10): 3072-3084

Summary: Systematic review to investigate the efficacy of probiotics in people with irritable bowel syndrome (IBS).

Conclusion: The results of the systematic review demonstrated the beneficial effect of probiotics on quality of life, abdominal pain, irritable bowel syndrome diagnostic scores and total symptoms. The results demonstrate the beneficial effects of probiotics in people with IBS in comparison with a placebo.

Paper: Liang D et al. Efficacy of different probiotic protocols in irritable bowel syndrome. A network meta-analysis. *Medicine* (2019) 98:27

Summary: Systematic review to differentiate therapeutic protocols by assessing the efficacy and safety through the combined methods of traditional and network meta-analysis.

Conclusion: Probiotics are a safe choice to improve the overall symptoms for people with irritable bowel syndrome.

Paper: Zhang Y et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. *BMC Gastroenterology* (2016) 16:62

Summary: Meta-analysis of randomized controlled trials to assess the efficacy of different probiotic types, doses and treatment durations in people with IBS diagnosed by Rome III criteria.

Conclusion: Probiotics are an effective therapy in people with IBS.

Paper: Hao Q et al. Probiotics for preventing acute upper respiratory tract infections (URTI). Cochrane Database Syst Rev. 2015 Feb 3;(2):CD006895. doi: 10.1002/14651858.CD006895.pub3.

Summary: Systematic review to assess the effectiveness and safety of probiotics in the prevention of acute URTIs in people of all ages at risk of acute URTIs

Conclusion: Probiotics were better than a placebo in reducing the number of participants experiencing episodes of acute URTI, the mean duration of an episode of acute URTI, antibiotic use and cold-related school absence. This indicates that probiotics may be more beneficial than a placebo for preventing acute URTIs. However, the quality of the evidence was low or very low.

Paper: Johnston B et al. Microbial Preparations (Probiotics) for the Prevention of Clostridium difficile Infection in Adults and Children: An Individual Patient Data Metaanalysis of 6,851 Participants. Infect Control Hosp Epidemiol. 2018 Jul;39(7):771-781

Summary: Meta-analysis of RCTs to determine whether probiotic prophylaxes reduce the odds of Clostridium difficile infection in adults and children.

Conclusion: Moderate quality evidence suggests that probiotic prophylaxis may be a useful and safe prevention strategy for Clostridium difficile infection, particularly among participants taking two or more antibiotics and in hospital settings where the risk of Clostridium difficile infection is $\geq 5\%$.

Paper: Huang R et all. Efficacy of Probiotics on Anxiety: A Meta-analysis of Randomized Controlled Trials. Neuropsychiatry (London) (2017) 7(6), 862–871

Summary: Meta-analysis of RCTs to assess the effects of probiotics on anxiety.

Conclusion: Probiotics decrease anxiety values in populations with anxiety.

Paper: Alfaleh K et al. Probiotics for prevention of necrotizing enterocolitis (NEC) in preterm infants (Review). *Evid.-Based Child Health* 9:3: 584–671 (2014)

Summary: Review to compare the efficacy of prophylactic enteral probiotics administration versus a placebo or no treatment in the prevention of severe NEC or sepsis, or both, in preterm infants.

Conclusion: Enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants. This updated review of available evidence strongly supports a change in practice.

Paper: Zimmermann P et al. The influence of probiotics on vaccine responses – A systematic review. *Vaccine* 36 (2018) 207–213

Summary: Systematic review of prospective randomised placebo-controlled studies in humans that have investigated the effect of probiotics on humoral vaccine responses

Conclusion: Probiotics offer a relatively cheap intervention to improve vaccine efficacy and duration. The suggestion that probiotics increase responses to influenza vaccination raises the possibility that probiotics might be helpful in elderly people, in whom it is known that seroconversion rates to influenza vaccination are lower in comparison to younger people.

Paper: Kerry R.G. et al. Benefaction of probiotics for human health: A review. *Journal of Food and Drug Analysis*, 26 (2018), 927-939

Summary: Review on the possible beneficial impact of supplementation with probiotics for human health.

Conclusion: Supplementation with probiotics, prebiotics, and synbiotics has shown promising results against various enteric pathogens due to their unique ability to compete with pathogenic microbiota for adhesion sites, to alienate pathogens or to stimulate, modulate and regulate the host's immune response by initiating the activation of specific genes in and outside the host intestinal tract. Probiotics have also been shown to regulate fat storage and stimulate intestinal angiogenesis.

Paper: Diez-Gutiérrez L. et al. Gamma-aminobutyric acid and probiotics: Multiple health benefits and their future in the global functional food and nutraceuticals market. *Journal of Functional Foods* 64 (2020), 1-14

Summary: Review of the research on probiotics and in particular focusing on gamma-aminobutyric acid, an important metabolite produced by many probiotic strains.

Conclusion: Many studies have proved the benefits of probiotics in *in vitro* and *in vivo* experiments. Investigations of the potential beneficial effects that metabolites produced by probiotics, including gamma-aminobutyric acid could have in humans is ongoing

Paper: Ohland C.L. et al. Microbial Activities and Intestinal Homeostasis: A Delicate Balance Between Health and Disease. *Cell Mol Gastroenterol Hepatol* 1 (2015) 28–40

Summary: Review discussing the equilibrium between host and microbial community in the context of health and disease. The focus is on bi-directional pressures between prokaryotes and eukaryotic cells, as well as inter-bacterial interactions resulting in alterations to the microbiota.

Conclusions: Disrupting of the dynamic environment of eukaryotic and prokaryotic cells in the gut has dire consequences for the host and may contribute to pathologies and disorders. Although there is value in defining which bacterial species are present in the gut, the field is moving toward regarding the enteric microbial community as an organ, rather than as individual parts.



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