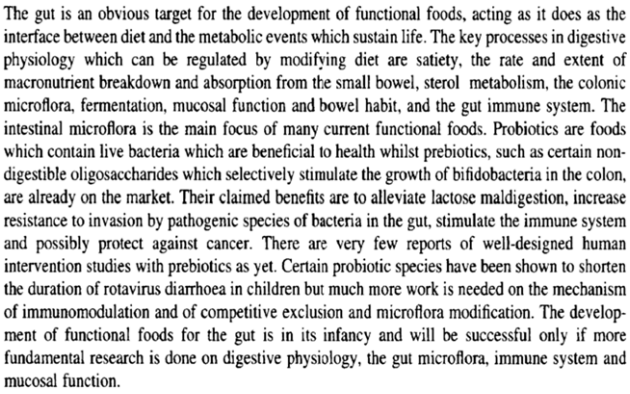
British Journal of Nutrition (2022), 128, 179–182 doi:10.1017/S0007114522001520

Invited Commentary

Commentary on: functional food science and gastrointestinal physiology and function



The gut is an obvious target for the development of functional foods, acting as it does as the interface between diet and the metabolic events which sustain life. The key processes in digestive physiology which can be regulated by modifying diet are satiety, the rate and extent of macronutrient breakdown and absorption from the small bowel, sterol metabolism, the colonic microflora, fermentation, mucosal function and bowel habit, and the gut immune system. The intestinal microflora is the main focus of many current functional foods. Probiotics are foods which contain live bacteria which are beneficial to health whilst prebiotics, such as certain non-digestible oligosaccharides which selectively stimulate the growth of bifidobacteria in the colon, are already on the market. Their claimed benefits are to alleviate lactose maldigestion, increase resistance to invasion by pathogenic species of bacteria in the gut, stimulate the immune system and possibly protect against cancer. There are very few reports of well-designed human intervention studies with prebiotics as yet. Certain probiotic species have been shown to shorten the duration of rotavirus diarrhoea in children but much more work is needed on the mechanism of immunomodulation and of competitive exclusion and microflora modification. The development of functional foods for the gut is in its infancy and will be successful only if more fundamental research is done on digestive physiology, the gut microflora, immune system and mucosal function.

Fig. 1. Screenshot of the abstract of the original highly cited paper[1].

Key words: **Gut physiology: Probiotics: Prebiotics: Synbiotics: Postbiotics**

Gastrointestinal physiology and function is a cornerstone target for functional foods. This was the basis of the 1998 British Journal of Nutrition review titled 'Functional food science and gastrointestinal physiology and function'[1]. An output of an International Life Sciences Institute – Europe working group, this article covered the basics of gastrointestinal function in health and disease through the lens of developing novel functional foods for health (Fig. 1). The article focused on probiotics and prebiotics as target functional ingredients. Importantly, this review was written before the explosion of data characterising the human microbiome. As microbiome science evolved, probiotics, prebiotics, synbiotics and more recently postbiotics (together the 'biotic' substances) as well as fermented foods were seen as potential tools that could improve health by modifying colonising microbiota composition, function or the gut environment. Although evidence that health effects are causally linked to biotics-induced changes in the microbiome are often lacking, the field has continued to promulgate under this hypothesis. The potential of these substances was recognised by food and pharma companies alike, with a resultant increase in research and product development. There have been conceptual advances in understanding shared mechanisms that may drive health effects of probiotics, which may ultimately lead to assignment of benefits to taxonomic groups broader than individual strains and biotic substances[2,3]. Continued mechanistic research is needed to provide a rational basis for selecting probiotics and other biotics[4], which may enable more effective design of human studies on functional foods required for demonstrating a health benefit. This commentary looks back at where we were at the time this article was published, where we are today and what the future may hold.

Quality and quantity of human interventions

Unfortunately, the zeal for the potential of biotic substances created an environment where too often marketing preceded the science. The review from 1998 acknowledges the paucity of well-designed human intervention studies for foods targeting the gut as a means of influencing health. Prior to 1999, there were only sixteen published (listed in PubMed) randomised controlled trials of probiotics in humans. Today, there are over 2500. For prebiotics, defined in 1995 by Gibson and Roberfroid[5], the respective numbers are zero and almost 700. Perhaps more important than the rise in numbers of publications is the overall improvement in the quality of human studies being published. In the 1990s, it was not uncommon to see studies on probiotics devoid of basic essential information, such as appropriate description of the intervention (strains and dose). Tracking and reporting of adverse events were uncommon, and trial reports often lacked clear descriptions of important study

Abbreviations: ISAPP, International Scientific Association for Probiotics and Prebiotics.

characteristics such as blinding, allocation concealment and compliance. However, today, trials of biotics are registered prior to recruitment (for example, at clinicaltrials.gov) and follow CONSORT guidelines for reporting[6]. A newer list of criteria for reporting microbiome-modulation studies, known as STORMS, is being promoted[7]. Together, these efforts reduce the risk of bias and increase the confidence in trial results.

Recent years have seen recommendations emerge for probiotics for some clinical conditions, even if some remain conditional and based on low-quality data. Recommendations for the use of probiotics to prevent necrotising enterocolitis[8], to treat colic in breast-fed infants[9], to prevent antibiotic-associated diarrhoea in adults[10] and children[11] and to prevent *C. difficile*-associated diarrhoea[8] have been published in recent years. Clinical recommendations for prebiotics, synbiotics or postbiotics are still lacking. Although there is still a great need for high-quality human studies to clarify the most effective interventions, doses and timing, progress has been made. There is also a great need to better understand likely responders to biotics interventions, taking into account differences in gut microbiota, diet, age and lifestyle.

The evolution and importance of definitions for scientific progress

An important development of the past decade has been the publication of definitions of the biotics family of terms (Table 1). These definitions were developed by consensus panels of experts convened by the International Scientific Association for Probiotics and Prebiotics(ISAPP). These panels applied several underlying principles in the development of the biotics definitions, including allowing for different mechanisms of action and not unduly limiting scope. Therefore, no definitions specify host, regulatory category or site of action. Since it was evident that these substances were intended to have utility as functional foods, functional ingredients or nutritional supplements, all definitions required a health benefit on a target host to be demonstrated. In addition, all definitions were limited to preparations that are administered and did not extend to substances produced by *in situ* activities, which would be adequately captured by the well-used term 'microbe-derived metabolites'. Regarding metabolites produced in products prior to end-use, definitions do not exclude their inclusion in preparations of probiotics, prebiotics or postbiotics, and certainly they may contribute to overall measured health impact.

In addition to the biotics definitions, ISAPP also defined fermented foods. Fermented foods, which have been a part of human diets since the Neolithic revolution about 14 000 years ago, may theoretically encompass all the biotics substances, as they supply us with microbes at various stages along the live–dead continuum, predigested nutrients and bacterial metabolites, all of which may affect human gut microbiota and the gut-associated immune system. Unlike the definitions for the biotics, fermented foods are restricted to human use and do not require demonstration of a health benefit.

The intention with publishing these definitions was to achieve harmonisation of the use of these terms by scientists, regulators, press and product marketers. A generally accepted definition for each member of the biotic family will hopefully help in creating regulatory clarity and promote innovation and the development of new health-promoting products.

Table 1. ISAPP consensus definitions for fermented food and biotics (probiotics, prebiotics, synbiotics and postbiotics). See https://isappscience.org/for-consumers/infographics/ for concise infographics describing all these substances

Term	Consensus definition
Fermented foods	Foods made through desired microbial growth and enzymatic conversions of food components[16]
Probiotic	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[3]
Prebiotic	A substrate that is selectively utilised by host microorganisms conferring a health benefit[17]
Synbiotic	A mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms that confers a health benefit on the host[12]
Postbiotic	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host[13]

During the development of the definitions, some points are interesting to highlight. The ISAPP's definition of probiotics came to endorse, with a slight linguistic adjustment, the WHO/FAO definition published by an expert consultation in 2001[3]. The 2017 definition of prebiotics updated the 1995 definition, making it more inclusive and more amenable to innovation. Whereas the 1995 definition focused on the promotion of a certain populations of gut microbes, more specifically lactobacilli and bifidobacteria, the 2017 definition was established to be included in the selective promotion of a wider range of microbes expected to promote health. For both definitions, the leading author was Prof. Glenn Gibson. For synbiotics, the 2020 definition updated the concept, clarifying the differences between a complementary and synergistic synbiotic[12]. As for the definition of postbiotics, several definitions that had been previously proposed were considered, but the consensus panel deemed them to be insufficient[13]. The final decision on the most appropriate and useful definition will rest with the scientific community and regulatory authorities.

Regulatory pressure

Regulatory requirements in the European Union became more rigorous with the establishment of the European Food Safety Authority, which was tasked to conduct scientific assessments of the highest standard for evaluating the safety of novel foods and the efficacy and health claims for foods. Since the establishment of the novel foods Regulation (EC) No 258/97, two new novel microbes have been approved in Europe (*Akkermansia muciniphila* and *Bacteroides xylanisolvens*). No health claims for probiotics have been approved since Regulation (EC) No 1924/2006 was enacted. Further, the standing Committee on the Food Chain and Animal Health in the guidance document on health claims, noting the requirement for a health benefit in the definition of the terms probiotic and prebiotic, concluded that using these terms on food labels constituted a *de facto* health

claim. They therefore determined that these terms could not be used on food labels in the absence of a health claim approved by European Food Safety Authority (—https://ec.europa.eu/food/system/files/2016–10/labelling_nutrition_claim_reg-2006–124_guidance_en.pdf). Similar logic will likely be applied to synbiotics and postbiotics. This approach has restricted information to consumers on biotics, while at the same time has allowed health claims, for example, for vitamins based on historical evidence rather than randomised controlled studies as is required for other health claims.

At the same time, an annually reviewed system of Qualitative Presumption of Safe assessment of microbes and biologicals approved in food has been established by EFSA[14]. This highly regarded approach serves globally as a safety assessment standard.

The future

In 1998, the gut was seen as the target for the development of functional foods. Within 10 years, the gut microbiota became the attribute of the gut that drew the most attention. Since that time, and reflected in the ISAPP definitions, other applications such as the skin, the oral cavity, vaginal tract, metabolic health and brain function became targets of interest. For many years, probiotics were developed from few genera, such as *Lactobacilliaceae*, *Bifidobacterium*, *Saccharomyces* or *Bacillus*, but the future see expansion of next-generation probiotic species, such as *Akkermancia muciniphila, Faecalibacterium prausnitzii*, *Prevotella copri* and *Christensenella minuta*[15]. Such developments may constitute an arsenal of probiotics, which in conjunction with traditional probiotics may enable more targeted use to likely responders. Biotic interventions have the potential to address challenges such as the increase of antibiotic-resistant pathogens or the microbiota disruptions caused by antibiotics and other medications resulting in the depletion of healthy microbiota. An important research question focuses on the extent biotics that may be able to improve the gut microbiota composition or function.

Acknowledgements

This commentary received no specific grant from any funding agency, commercial or not-for-profit sectors.

All authors contributed equally on the manuscript.

S. S. serves on the board of ISAPP and has been a speaker in meetings funded by Industry and Institute Danone. G. V. is a member of the Argentinian board of the Yoghurt in Nutrition Initiative (YINI, Argentina) and the board of ISAPP. M. E. S. is the executive science officer of ISAPP. M. E. S. has been compensated for consulting or service on advisory boards by Bayer, Bill and Melinda Gates Foundation, California Dairy Research Foundation, Church & Dwight, Georgetown University, Pepsico, Smith, Gambrell & Russell LLP, Cargill, Danone North America, Danone Research, Sanofi, Winclove Probiotics and Yakult. She has also been compensated for giving presentations for Kerry, Associated British Foods, Mead Johnson, Fairlife, GlaxoSmithKline, Trouw Nutrition, Omnibiotic/Allergosan, Probi, Sanofi and European Federation of the Associations of Dietitians. She has provided uncompensated service or been reimbursed for travel funding for non-profit organizations, USP, ILSI-NA/IAFNS and Nebraska Food for Health Center.

Seppo Salminen[1]*, Gabriel Vinderola[2] and Mary Ellen Sanders[3]

[1]Functional Foods Forum, Faculty of Medicine, University of Turku, Turku, 20014, Finland
email sepsal@utu.fi

[2]Instituto de Lactología Industrial (INLAIN, UNL-CONICET), Facultad de Ingeniería. Química, Universidad Nacional del Litoral, Santa Fe, Argentina

[3]International Scientific Association for Probiotics and Prebiotics, Centennial, CO, USA

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