

Probiotics Reference

YOGHURTS & FERMENTED MILKS

Newsletter
of SYNDIFRAIS
science committee

Market supply of probiotic dairy products and scientific publications show parallel increase



In 2006, around the world, there were no fewer than 827 dairy products containing probiotics on the market (Meyer H-L, 2007). Yoghurts and other fermented milks were the driving force, accounting for 90% of supply, far ahead of baby preparations (4.3%), cheeses (2.7%) and milks (2.4%). New products have been appearing at a steadily increasing pace for a number of years, and this increase correlates with an explosion in the number of scientific publications on probiotics (Figure 1). While analysis of the literature shows that the research concerns a wide variety of bacterial strains, the range used in commercial products is still fairly narrow: only 39 strains are to be found on product labels (when the strain is specified) and six of these cover nearly three-quarters of all products between them.

The small number of strains used is certainly partly due to the amount of resources manufacturers have to invest to provide scientific proof of the benefits of their products under current European regulations on health claims. Validating a probiotic strain is a long process involving major financial investments, especially when it involves clinical trials. But rapid progress is being made in this field too, as the scientific literature reveals: the annual number of publications reporting on clinical trials has increased five-fold since 2000. Articles on human trials now amount to 12% of all published articles on probiotics.

Analysis of international scientific publications is an essential task for apprehending the rapid development of the probiotics field and - why not - attempting to infer a trend for the next few years. On pages 2 and 3 of this issue of Reference Probiotics we offer a few reference data.

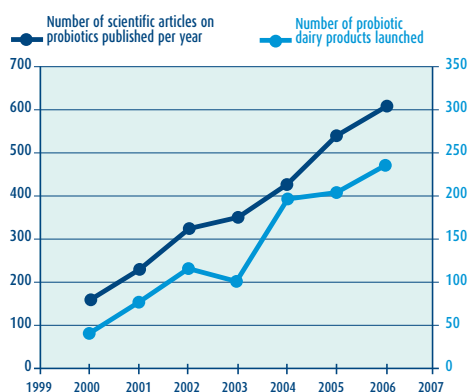
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Figure 1: Annual launches of probiotic dairy products (all countries) and annual number of publications on probiotics.



Product launches and the number of articles published annually are increasing constantly and jointly. Between 2000 and 2006, the number of probiotic dairy product launches increased almost sixfold. Over the same period, the number of scientific articles published per year increased fourfold.

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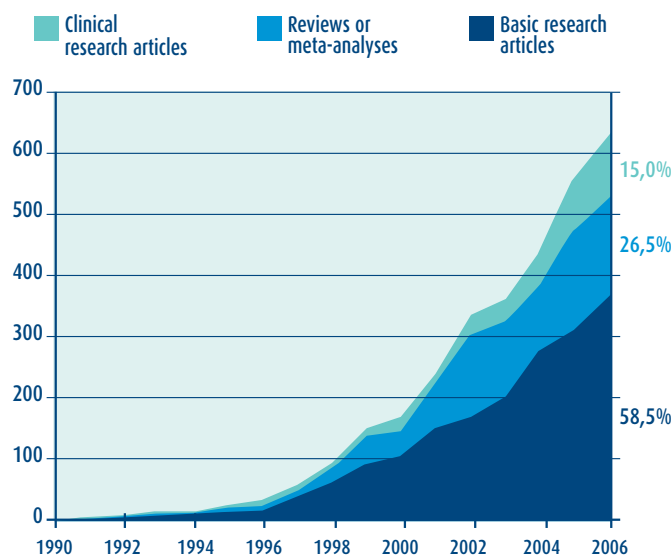


... Bibliometric references on probiotics

The NCBI's Medline bibliographic database was searched to monitor trends in the scientific literature on probiotics over the period 1990-2006. A keyword search was conducted on titles and/or abstracts. In some cases the abstracts were read in full for a more detailed analysis. Below we present and comment on some of the more striking findings from this bibliometric study.

The total number of publications dealing with probiotics multiplied almost 140-fold over a period of 16 years. Since the late 1990s, the proportion of basic research articles has declined slightly and in 2006 they represented only about three articles in five (Figure 1). They have made way for publications reporting on clinical trials, which account for a steadily increasing proportion of the total. Overview publications - mainly reviews, and a smaller number of meta-analyses - make up a large proportion of the total. That proportion was 35% in 2002 and 40% in 2003, but has since declined and seems to be stabilising at around 27%.

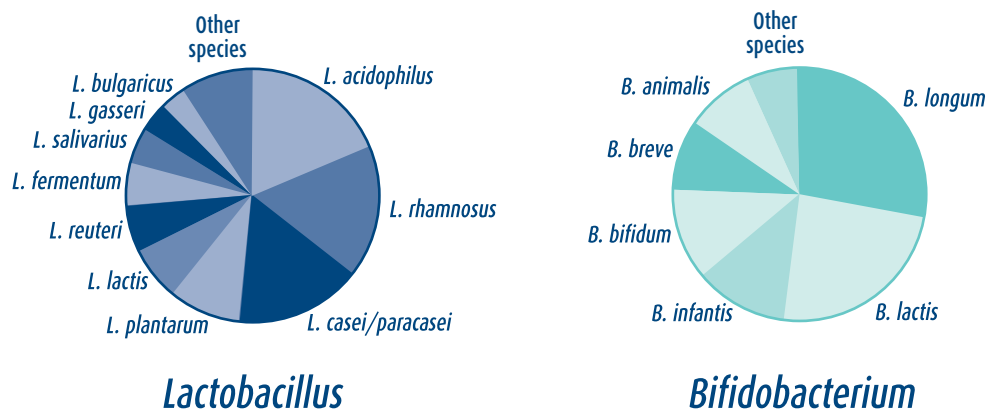
Figure 1:
Number of articles on probiotics published annually



In 1989 the Medline database included fewer than 25 publications on probiotics. By the end of 2006 it had over 3,000. The constant acceleration in the pace of publications should result in an output of 700 new articles in 2007.

Most articles on probiotics deal with lactobacilli and bifidobacteria (49% and 21% respectively, excluding review articles). The remaining 30% of articles concern other bacterial genera (yeasts, propionic bacteria, *enterococci* and *Escherichia coli* Nissle 1917), but mostly concern mixtures of probiotic strains or commercial preparations whose species are not explicitly described in the publications. While the *Lactobacillus* and *Bifidobacterium* genera include many different species, most studies concern a fairly small number of species and quite often the same strains (Figure 2).

Figure 2:
Most widely studied species of Lactobacilli and Bifidobacteria



Of all the wide variety of *Lactobacillus* species, *L. acidophilus*, *L. rhamnosus* and *L. casei/paracasei* between them account for more than half of all publications on probiotic lactobacilli. *B. longum* and *B. lactis* each account for a quarter of published articles on probiotic bifidobacteria.

Analysis of papers published in the past 18 months shows that digestive disorders are still the main field for probiotics research, accounting for 26% of research papers. The sum of scientific data accumulated over the past 20 years in this field certainly explains the large number of literature reviews devoted to these disorders (39%), and the particularly high proportion of clinical studies they represent (Table 1).

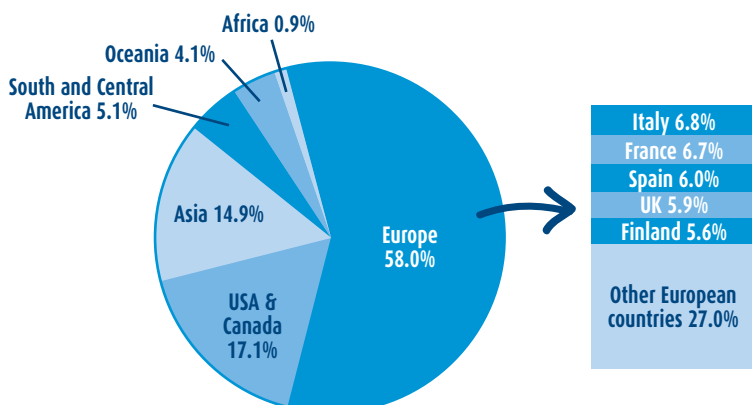
The second most studied field for probiotics is immunity, with 23% of research papers, but only 9% of the review articles. Most of the topics addressed concern allergies and immunomodulation.

A growing number of new fields of probiotic action are emerging in the literature. Although most of the new topics addressed are still at the exploratory research stage (*in vitro* studies and sometimes animal studies), some topics have been the subject of more advanced research with a certain number of published results. These include uro-genital disorders, oral health, weight control and growth.

Probiotics' fields of action in digestive disorders	Type of publications		
	Clinical trials	Studies with animal models	<i>In vitro</i> studies
• Inflammatory intestinal diseases <i>(42% of publications on the field of intestinales disorders)</i> - irritable bowel syndrome - colitis	47%	47%	6%
• Diarrhoea <i>(21% of publications in the field of intestinal disorders)</i> - antibiotics diarrhoea - acute diarrhoea	81%	19%	0%
• Digestive pathogens <i>(11% of publications in the field of intestinal disorders)</i> - <i>H. pylori</i> infection	63%	12%	25%
• Other <i>(26% of publications in the field of intestinal disorders)</i>	10%	55%	35%

For some types of disorder, the degree of progress in research is reflected in a high proportion of clinical research papers. Analysis of 407 papers on probiotics published in 2006 and the first half of 2007.

Europe is particularly active in probiotics research, producing 58% of world publications (Figure 3). North America and Asia together account for 32% of papers. While the proportion of European publications has remained relatively stable over time, Asian output accounts for an increasing proportion while North America's share has been shrinking.



Between them, just five European countries account for one-third of the scientific literature on probiotics.

Table 1: Nature of publications on the action of probiotics on digestive disorders

Figure 3: Geographical origin of publications on probiotics

New clinical trials

A Finnish clinical study published in 2001 suggested that one probiotic strain had a preventive effect against allergic diseases [1]. In that trial, strain *Lactobacillus rhamnosus* GG (LGG) was administered to pregnant women who had at least one first-degree relative (or partner) with an allergy, then to the infant for 6 months. The children were followed up to the age of 2. The results suggested a significant reduction in the incidence of eczema. A recent re-examination of the children, now 7 years of age, has confirmed these results (Table 1), [2].

Three other clinical trials based on similar protocols have been published recently [3-5]. Their results are varied, differing from each other and from the Finnish study (Table 1). These substantial differences may particularly be linked to the use of different probiotic strains, but dosage and duration of administration and the administration of a prenatal probiotic treatment to the mother could all play a significant role. At all events these results call for further research to assess the usefulness of probiotics for allergy prevention.

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Table 1: Protocols and main results of four clinical trials assessing the effects of probiotics on the prevention of allergic diseases

	Authors			
	Kalliomäki <i>et al.</i> [2]	Abrahamsson <i>et al.</i> [3]	Kukkonen <i>et al.</i> [4]	Taylor <i>et al.</i> [5]
Characteristics of the probiotic preparation used	- Capsule containing <i>L. rhamnosus</i> GG - Dose: 10 ¹⁰ CFU/d (mother and infant)	- Suspension of <i>Lactobacillus reuteri</i> ATCC55730 - Dose: 10 ⁸ CFU/d (mother and infant)	- Capsule containing <i>L. rhamnosus</i> GG (5x10 ⁹ CFU) and LC705 (5x10 ⁹ CFU), <i>Bifidobacterium breve</i> Bb99 (2x10 ⁸ CFU), <i>Propionibacterium freudenreichii</i> JS (2x10 ⁸ CFU) - Dose: 2 capsules/d (mother); 1 capsule/d + 0.8g of galacto-oligosaccharides (infant)	- Sachet of powder containing <i>L. acidophilus</i> LAVRI-A1 - Dose: 3x10 ⁹ CFU/d (infant only)
Administration period	- Mother: from 4th week before expected delivery to 6 months after the birth - Infant: from 0 to 6 months (+ follow-up to 7 yrs)	- Mother: from 4th week before expected delivery to birth of child - Infant: from 0 to 12 months (+ follow-up to 2 yrs)	- Mother: from between 2 and 4 weeks before birth until the birth - Infant: from 0 to 6 months (+ follow-up to 2 yrs)	- Mother: no treatment - Infant: from 0 to 6 months (+ follow-up to 1 yr)
No. of patients at end of study	- Probiotic group: 62 - Placebo group: 53	- Probiotic group: 95 - Placebo group: 93	- Probiotic group: 461 - Placebo group: 464	- Probiotic group: 89 - Placebo group: 89
Incidence of eczema	Lower in the probiotic group (P=0.008)	No difference between the two groups	Lower in the probiotic group (P=0.035)	Not evaluated
Incidence of atopic eczema	No difference between the two groups	Lower in the probiotic group for infants aged 1 to 2 (P=0.02), from 6 months for children of allergic mothers (P<0.01).	Lower in the probiotic group (P=0.025)	No difference between the two groups
Sensitization to allergens	No difference between the two groups	Lower in the probiotic group for infants aged 1 to 2 (P= 0.09), all ages for children of allergic mothers (P<0.01)	No difference between the two groups	Higher in the probiotic group (P= 0.03)
Incidence of other allergic diseases	Higher in the probiotic group for allergic rhinitis and asthma (non-significant trends)	No difference between the two groups	No difference between the two groups	No difference between the two groups

Few studies so far have focused on the analgesic effects of lactic acid bacteria [6-8]. Recent studies confirm that it may be possible to use probiotics to treat abdominal pain such as that suffered by patients with irritable bowel syndrome [9].

The authors first sought to confirm the hypothesis that probiotic bacteria could induce expression of analgesic receptors in the epithelial cells of the colon. Of five *bifidobacterium* and *lactobacillus* strains placed in the presence of HT-29 cells in culture, *L. acidophilus* strain NCFM proved capable of stimulating the expression of two types of analgesic receptors: the μ 1 opioid receptor (MOR1) and the cannabinoid receptor CB2. The experiments also show that expression of the same receptors is induced in rats and mice to which the bacterial strain has been administered (10^9 CFU.d⁻¹ for 15d), confirming *in vivo* with animals what had been observed *in vitro*.

The authors then tried to show a functional response to the induction of these receptors. The perception of pain following colorectal distension was measured in rats treated and not treated with strain NCFM. The results show that the pain perception threshold rose significantly ($P < 0.01$) after 10 days' daily administration of the probiotic. The effect was dose-dependant. This analgesic effect was maintained for as long as the treatment continued and was equivalent to a subcutaneous administration of 1mg of morphine per kg body weight.

By showing that the interactions between lactic acid bacteria and epithelial cells can modify intestinal pain modulation, this research opens up promising therapeutic prospects. Hopefully, the clinical investigations will draw the same conclusions.

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A study published in 2002 had shown with human and mouse intestinal epithelial cells in culture that *Lactobacillus rhamnosus* GG (LGG) could prevent certain apoptosis processes [10]. That study suggested that soluble factors produced by the bacterium were responsible for the observed antiapoptotic effects. A new study has shed light on the results of that preliminary work by identifying the soluble factors concerned and the bases for an action mechanism [11].

First, the two majority proteins in the LGG culture supernatant (p40 and p75) were purified. Analysis of their nucleic and protein sequences showed close similarities with the sequences of two proteins of *L. casei* strain 334, whose functions are unknown.

Each of the proteins p40 and p75 were then placed in the presence of either epithelial cells in culture or colon explants to evaluate their effects on apoptotic processes. Both proteins gave rise to the same observations:

- 1) kinase-dependent activation of factor Akt that negatively regulates an apoptosis signalling pathway and inhibition of caspase 3, which is involved in the same pathway;
- 2) changes in the main histological parameters with a regression in the apoptosis process induced by proapoptotic cytokines (TNF, IL-1, INF γ);
- 3) restoration of the epithelial integrity of colon explants damaged by a process of apoptosis and significant reduction in the number of apoptotic cells in the crypts;
- 4) stimulation of epithelial cell growth by a factor of about 2.5.

To date, LGG proteins p40 and p75 are the only examples of soluble bacterial proteins found to regulate homeostasis in intestinal epithelial cells by a specific signalling pathway. However, LDD does not seem to be the only bacterium to secrete this type of protein. The same study revealed that proteins with similar functionalities are secreted by *L. casei* strains 334 and 393.

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Lactobacillus acidophilus modulates pain via analgesic receptors

Proteins secreted by LGG inhibit apoptosis and stimulate cell proliferation

In vitro / in vivo correlation

A team at the Institut Pasteur in Lille, France, studied the relationship between the capacities of 12 strains of lactic acid bacteria to modulate cytokine secretion by cells in culture¹ and the potential effects of these strains on the symptoms of mice with colitis² [12]. For all the strains tested, the results show that the IL10/IL12 ratio determined *in vitro* correlates with the scale of the anti-inflammatory effects observed *in vivo*. The methodology used seems to offer a simple and fairly easily reproducible tool for pre-selecting strains with immuno-modulating properties. Other strains are being screened to validate the method's predictive character and build up a reference database. The method should soon be evaluated for strains whose clinical efficacy has been proven.

(1) Peripheral blood mononuclear cells (PBMC)

(2) Model of acute colitis induced by TNBS (trinitrobenzene sulfonate).

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Yoghurt and the digestive microbiota

Scientists recently studied the impact of yoghurt consumption on the composition and metabolism of the faecal microbiota [13]. Thirty subjects consuming 200 to 400g of yoghurt a day as part of their usual diet were compared with 22 subjects consuming no yoghurt. The results showed no notable difference between the two groups in terms of microbiota composition, except that part of the yoghurt-consuming group had a significantly lower level of enterobacteria¹ (P=0.006). A positive correlation was also observed between yoghurt consumption and the bifidobacteria population. As regards metabolism, only a significant increase in the activity of fecal β -galactosidase (lactase) was shown in the yoghurt-consuming group. This activity also showed a positive correlation with yoghurt consumption.

(1) The enterobacteria group includes a number of pathogenic bacteria.

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Synbiotics and colon cancer

Many data from animal or *in vitro* models suggest that pre- and pro-biotics protect against the development of colon tumours. A study involving 37 colon cancer patients and 43 polypectomised patients suggests that the same may be true for humans [14]. In the group treated with a synbiotic mixture¹, several characteristic biomarkers seem to have developed positively (composition of faecal microbiota, colonocyte DNA damage, proliferative activity in the crypts, etc.). Another study, using the same type of synbiotic, draws different conclusions on the improvement of immune parameters [15].

(1) Mixture of *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb12 and oligofructose with added inulin.

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Dendritic cells

The results of one study show that intraperitoneal administration of dendritic cells pre-stimulated by lactobacilli to mice with TBNS-induced colitis attenuates the inflammation and several symptoms associated with the pathology [16]. The expression of cytokine genes and pro-inflammatory factors were also greatly reduced. The study also shows that the mechanism concerned involves T-regulator cells (CD4+ CD25+) and specific receptors (TLR2; NOD2).

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Propionibacteria: future probiotics?

Three strains of *Propionibacterium freudenreichii* previously selected *in vitro* for their tolerance to acid stress and their ability to produce propionic acid were administered for 20 days to rats colonised by a human microbiota [17]. All three strains showed high survival rates in caecal and faecal contents (up to 3×10^6 CFU.g⁻¹) as well as transcriptional activity. One strain also increased concentrations of short-chain fatty acids in the caecum. Given these promising features, propionibacteria must now give proof of their probiotic properties.

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If it's not viable it's not probiotic

A group of researchers have criticised authors who use the term "probiotic" improperly, to refer to nonviable bacterial preparations [18]. Under FAO recommendations, a probiotic must not only be of identified genus and species. The strain must be identified and have been characterised functionally. It must have been investigated in humans, and a health benefit must be proven.

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Probiotics Reference

YOGHURTS & FERMENTED MILKS

... THE SCIENCE COMMITTEE

Its mission

- The Syndifrais science committee brings together scientists and researchers from universities and from the fresh milk products industry.
- It is an independent body which seeks out and publicises scientific evidence of the health benefits and harmlessness of the live lactic acid bacteria in yoghurt and fermented milks.
- One of its tasks is to make a critical scan of the literature on the physiological action of probiotics and the mechanisms of such action. The results of this science survey are published in the newsletter Probiotics Reference.

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Spotlight on



Functional dairy products - vol. 2

To update the first volume, published in 2003⁽¹⁾, a second volume on functional dairy products has just been published, edited by Maria Saarela⁽²⁾.

The book reviews this constantly-developing field in 24 chapters. The first part covers the health benefits of functional dairy products (e.g. weight control, health of the digestive tract). The second part addresses functional dairy ingredients (e.g. probiotic propionibacteria, synbiotics, products containing plant stanols and sterols).

The last part highlights product development (e.g. regulations, experimental models, molecular approaches and functional genomics, technological aspects and microorganism safety), including examples of products on the market.

(1) **Mattila-Sandholm T & Saarela M, Eds. (2003)**. Functional dairy products. CRC Press, Woodhead Publishing Ltd. Cambridge, England. 395p.

(2) **Saarela M, Ed. (2007)**. Functional dairy products, volume 2. CRC Press, Woodhead Publishing Ltd., Cambridge, England. 539p.

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