Functional foods in pediatrics

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Abstract

The philosophy that food can be health promoting beyond its nutritional value is gaining acceptance. Known disease preventive aspects of nutrition have led to a new science, the 'functional food science'. Functional foods, first introduced in Japan, have no universally accepted definition but can be described as foods or food ingredients that may provide health benefits and prevent diseases. Currently, there is a growing interest in these products. However, not all regulatory issues have been settled yet. Five categories of foods can be classified as functional foods : dietary fibers, vitamins and minerals, bioactive substances, fatty acids and pro-, pre- and synbiotics. The latter are currently the main focus of research. Functional foods can be applied in pediatrics : during pregnancy, nutrition is 'functional' since it has prenatal influences on the intra-uterine development of the baby, after birth, 'functional' human milk supports adequate growth of infants and pro- and prebiotics can modulate the flora composition and as such confer certain health advantages. Functional foods have also been studied in pediatric diseases. The severity of necrotising enterocolitis (NEC), diarrhea, irritable bowel syndrome, intestinal allergy and lactose intolerance may be reduced by using functional foods. Functional foods have proven to be valuable contributors to the improvement of health and the prevention of diseases in pediatric populations. (Acta gastroenterol. belg., **2002**, 65, **45-51**).

Key words : probiotics, prebiotics, functional foods, flora, pediatrics.

Introduction

'Let food be your medicine and medicine be your food' was a tenet of Hippocrates in approximately 400 before Christ. In earlier days, food was mainly considered to be an energy supplier, only needed to meet metabolic and nutritional requirements of human beings. After the second world war, welfare raised incredibly and general food patterns changed. Since then, the combination of excessive food intake and a decreased physical activity became a new threat for Western populations leading to an increasing prevalence of chronic 'welfare' diseases. Current feeding patterns are characterized by a higher intake of saturated fats and a lower intake of complex carbohydrates. In the 1980s, the idea of 'adequate nutrition' has evolved towards 'optimal nutrition'. We were becoming increasingly aware that certain foods or constituents within foods may promote health. Preventive aspects of nutrition and evidence based statements such as '*increased consumption of fruit and vegetables is accompanied by a reduced risk of heart disease and cancer*' (1-4) were the start of the concept of functional foods (5). Moreover, advances in food science and technology can now provide the food industry with sophisticated methods to develop new nutrients and nutrient components. The current interest in functional foods started in Japan. 'Foods for specific health use' were approved in 1991 and initiated the 'functional food science'. Since then, considerable interest in functional foods also exists in the US and Europe. Fermented milk products with live bacteria have been consumed for centuries, however, the interest in the use of live microbial agents for the purpose of health maintenance and disease prevention or treatment has exploded over the last few years.

Definition

At present there is no universally accepted definition for functional foods. An action coordinated by the International Life Sciences Institute (ILSI) Europe on functional foods in Europe (EUFOSE), involves collaboration of more than 40 experts from the public sector and the food industry. According to ILSI, *a food can be regarded as 'functional' if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease.*

A product can be made functional by increasing the concentration of a natural component, by adding a component that is not contained in most foods or only in trace amounts, by replacing a component that may have deleterious effects or by improving the bioavailability of food components.

Functional foods must remain foods and must show effects when consumed in normal amounts. This suggests that the definition excludes dietary supplements in the form of a pill, tablet or capsule. Functional foods or food components should also be safe : if novel ingredients are intentionally added, such as e.g. a component to fortify a processed food, their safety must be evaluated according to rules established for that new category of foods (5-11).

Claims

Regulations regarding commercialization are currently unclear. This is partly due to a lack of scientific background, important for the development of functional

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foods, due to the lack of clinical trials necessary to demonstrate their positive effects, due to the costly adequate quality control and the need for demonstration of safety. Discussion within European countries have emphasized different approaches. Medicinal claims may definitely not be accepted. The claims may not be false or misleading and should voice a generally recognized action or effect of a nutrient or a food component. The system used in North America to categorize foods or drugs has been a classification model based on food and drug use definitions. However, this model became difficult to apply and it may be important to view the products with regard to promoting health, reducing risk of or preventing disease. In the United States, legislation appears to favor the development of functional foods in the form of dietary supplements. Food labeling in Canada is undergoing revision to permit nutrient content claims but health-related claims are illegal (7).

Candidate functional foods

The component that makes the food 'functional' can be either an essential macronutrient if it has specific physiologic effects, or an essential micronutrient if its intake is over and above the daily recommendations. Additionally, it could be a food component even though some of its nutritive value is not listed as 'essential' (e.g. oligossaccharides) or it is even of non-nutritive value (e.g. live microorganisms). So far, 5 areas of functional foods have been described in detail : dietary fibers, vitamins and minerals, bioactive substances, fatty acids and pro-,pre- and synbiotics. These groups all have demonstrated beneficial effects for the host. Intake of dietary fibers (e.g. pectins) reduces total cholesterol, LDL-cholesterol and serum lipids. They have a favorable effect on glucose and insulin sensitivity and are known to ameliorate constipation. Fibers can be found in cereals, fruit juices, etc. Some vitamins such as vitamin A, E and C are known as antioxydantia. Intake of adequate amounts of calcium and vitamin D are indispensable to reduce the risk of osteoporosis. A low intake of potassium will increase the risk for hypertension and therefore, extra potassium can preventively lower blood pressure, especially in subjects who are unable to lower their sodium intake. Additional amounts of vitamins and minerals can be found in fruit juices, cereals and dairy products. Fatty acids, such as ω-3 and ω-6 fatty acids are important for blood coagulation and for lowering LDL-cholesterol and triglycerides. They can be found in margarines, oils and baby products. Bioactive substances such as polyfenols, flavonoids, found in drinks, dairy drinks and soy products, are known to be anti-hypertensive and anticarcinogenic.

Pro-, pre- and synbiotics are terms introduced in the 1970s to describe food supplements that are either viable organisms or substrates influencing the microenvironment of the host.

According to Fuller (12), a probiotic is defined as '*a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance*'. Specific criteria must be met for a food supplement to be qualified as a probiotic : it must be capable of being prepared in a viable manner and on large scale, it should remain viable and stable, it should survive in the intestinal ecosystem and the host should gain benefice from harbouring the probiotic.

Examples of probiotics are *Lactobacilli, Bifidobacteria, Streptococci* and *Saccharomyces*. Clinical trials with probiotics show a decreased incidence and severity of diarrhea, a stimulation of the host immune system, a lowering of serum cholesterol, metabolization of lactose in lactase-deficient individuals and an inactivation of bacterial enterotoxins (13).

A pre-biotic is '*a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health*'. A prebiotic should not be hydrolyzed nor absorbed in the upper gastro-intestinal tract, it must be a substrate for beneficial bacteria in the colon and it must be able to alter the colonic flora in favor of a healthier composition. Examples of prebiotics are galacto- or fructo-oligosaccharides (GOS–FOS), such as inulin and oligofructose. Prebiotics have an effect on colonic microflora, mineral absorption, lipid metabolism and have interactions with the carcinogenesis process and immunology.

A synbiotic is '*a mixture of pro- and prebiotics which beneficially affects the host and improves health by adding dietary supplements in the gastrointestinal tract*'.

Pro-, pre- and synbiotics can be found in yoghurt, fermented milk, margarine, cereals, baby milkproducts and bakery products.

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Prenatal influences of functional foods

Protein enriched diets during pregnancy may be beneficial for the prevention of pregnancy-induced hypertension and pre-eclampsia (14,15). Maintenance of health during the course of pregnancy requires also an adequate supply of vitamins and minerals, some of particular significance. Folic acid intake has to increase in response to the demands of maternal erythropoiesis and fetal-placental growth. Folic acid is essential for the synthesis of pyrimidines, purines and thus of DNA and RNA. Poor folic status has been associated with neural tube defects (16-18). A marked increase in the maternal blood volume during pregnancy greatly increases the demand for iron. Iron deficiency remains a problem during pregnancy and can lead to maternal and fetal morbidity and mortality. Minerals such as magnesium, zinc and iodine are also proposed to be added to the maternal diet to prevent respectively eclampsia, low birth weight, miscarriages, preterm delivery and cretinism (19-21).

Postnatal influences of functional foods

At birth, the human neonate exchanges two fluids of closely regulated composition (maternal blood and amniotic fluid) for a third fluid (maternal breast milk or formula feeding). Human milk provides all necessary nutrients to support adequate growth of the newborn during the first months of life. Many factors in colostrum and breast milk promote adaptation to extra-uterine life (22). The difference in flora between breast-fed and formula fed infants is thought to play a role in the protective effect of breast milk. Human milk also contains enzymes, growth factors, antibodies and anti-infective factors. The exact roles of these specific components are not all clarified yet but are interesting subjects for further development of functional foods. It also contains galacto-oligosaccharides which have been demonstrated to favor the growth of bifidobacteria, a commonly used probiotic. Therefore, breast feeding protects the infant when gut microflora and gut immunological defense mechanisms become established.

The infants' intestinal microflora, an important constituent of the gut defense barrier, is an obvious target for the development of functional foods, since it has been demonstrated that differences in gut microflora affect immunological homeostasis of the host. Prior to birth, the gastrointestinal tract is sterile. Massive and rapid colonization of the digestive tract of infants by micro-organisms is part of the adaptation to extra-uterine life. The first two days after birth are characterized by the predominance of a few bacteria, e.g. *E. coli* and *Enterococci*, that are the first bacteria to colonize the gut (23-26). At the end of the first week an equilibrium is found depending of the type of feeding. Eighty five percent of breast-fed infants harbour *Bifidobacteria* as predominant microorganisms, while in formula fed infants *Bifidobacteria* are associated with other species such as *Clostridia*, *Bacteroides* and *Streptococci* (27, 28). After weaning, the flora is changed into a pattern that resembles the adult flora (29). The human gastrointestinal tract is an intense site of microbial activity. At least 500 different microbial species exist, from which 10-20 genera probably predominate.

A major role of the intestinal microflora consists of protecting the newborn or infant against the invasion of pathogens. However, various dietary, emotional and environmental stresses, as well as infections, antibiotics,... may cause changes in gut flora throughout life (30-32). A new trend has therefore arisen to produce foods that stimulate the growth or activity of beneficial microorganisms in the intestinal tract. Pro-, pre- and synbiotics modulate the flora composition and confer health advantages. The commonest probiotics, *Bifidobacteria* and *Lactobacilli*, and prebiotics, galacto- and fructo-oligosaccharides have anti-pathogenic characteristics, are responsible for colonization resistance in the gut and stimulate the immune response.

Currently, many research efforts are pointed towards elucidating the effect that beneficial bacteria may have on gut immunologic response and its systemic consequences. The possibilities of receptor competition, increased mucin secretion, bacterial 'priming' of gut associated lymphoid tissue (GALT), and immuno modulation of GALT response are all being considered.

Food or food supplements containing pro- or prebiotics

Interest in functional foods, especially pro- and prebiotics, is growing increasingly and has already a major impact on the food and drinks market. Various foods or food supplements have been commercialized. Table 1 gives an overview of some products containing pro- or prebiotics. This table however, is not complete.

Also infant formula feedings containing pro- or prebiotics have recently become available : BIO NAN® (Nestlé) with *Lactobacillus bifidus* as probiotic, NAN 2 bifidus® (Nestlé) with *Bifidobacterium Lactis* B_L and

Table 1. — **Food or food supplements containing pro- or prebiotics**

Product	Manufacturer	Pro- or prebiotic
Actiline®	Vandemoortele	Inulin
Nutridrink fibre®	Nutricia	Inulin
Sveltesse®	Nestlé/Chambourcy	Inulin
Taillefine yogurt®	Danone	Oligofructose
Instaslim® bars and powders	Omega Pharma	Oligofructose
Vitalinea® yogurt and meal	Danone	Inulin
Menu Minceur®	Yoplait	Inulin
LC1 fermented milk®	Nestlé/Chambourcy	L acidophilus
Yakult® fermented milk	Yakult	L caseii Shirota
Danone Bio®	Danone	L caseii GG
Provie® fruit drink	Provie	L plantarum 299v
Actimel®	Danone	L caseii imunitass
Vifit®	Stassano	L caseii GG
Colon Clean®	Pharmafood	L acidophilus
Proflora®	Chefaro	L acidophilus, L bulgaricus, S thermophilus, Bifidobact
Probiotic plus®	Biodynamics	L acidophilus

Streptococcus thermophilus as probiotics ; Omneo® (Nutricia), Conformil® (Milupa) and Omneo Confort® (Cow and Gate) with FOS and GOS as prebiotics.

BIO NAN® (Nestlé) is a formula for infants from birth on. The infant feeding is acidified by fermentation with *Streptococcus thermophilus* and *Lactobacillus helveticus*. It is also enriched with *Lactobacillus bifidus* and therefore results in an optimalisation of the microbial flora ('bifidogenic effect') and prevention against infections. Nestlé also developed a follow-up formula feeding for infants (4-18 months), NAN 2 bifidus®. This formula is enriched with two probiotic strains : *Bifidobacterium Lactis* B_L and *Streptococcus thermophilus*. These bacteria resist an acidic gastric environment, survive the gastrointestinal tract and can be stored in formula powder. *S. thermophilus* has a known lactase activity (33).

A clinical trial conducted by Langhendries et al compared a group of infants who received BIO NAN® enriched with *B Lactis* B_L and *S. thermophilus* and *L. helveticus*, a group of breast fed infants and a group of infants fed non-enriched formula (34). Results demonstrated that the first group had a significantly higher amount of *Bifidobacteria* in their stools. Saavedra *et al.* studied in a double blind, placebo controlled study, 55 hospitalized infants who received NAN Bifidus B_L® or a conventional non-enriched formula (NAN 2®). Results of this trial showed a lower incidence of diarrhea in the group of hospitalized infants who received the enriched formula (6.9 vs 31%). The prevalence of rotavirus also was diminished (10.3 vs 38.5%) (35).

Numico (Nutricia, Milupa, Cow and Gate) introduced Omneo®, Comformil® and Omneo Comfort®, being a similar formula for infants (0-18 months). The formula combines several components which can be expected to help alleviate common feeding problems. The fat source contains structured vegetable oils mimicking human milk fat by providing palmitic acid esterified in the n-2 position. This may result in improved fat absorption and softer stools (no calcium soap formation). The protein source is a partially hydrolyzed whey protein. Also pregelatinised potato starch for satiety has been added. The novel components of the formula are oligosaccharides. Human milk contains approximately 1% oligosaccharides. Since analogues of the very complex human milk oligosaccharides are not commercially available, a mixture of GOS and FOS has been developed for the formula. Preliminary clinical trials conducted with preterm and term infants confirm that this mixture (9 parts GOS – 1 part FOS, 1g FOS/GOS per 100 ml) has bifidogenic properties and has good acceptability characteristics (Boehm *et al*., unpublished data).

The above mentioned infant formula feedings, enriched with pro- or prebiotics, were developed in an effort to approach more closely the gold standard, human milk. Nevertheless one remark has to be added. The effect of pro- and prebiotics is only temporary and strictly related to intake.

Although numerous studies in adults and animals suggest a beneficial effect on host flora (36-39), only preliminary and unpublished data are available from infants at the present time.

Role of functional foods in pediatric diseases

Modification of intestinal flora to increase the predominance of non-pathogenic bacteria seems a reasonable alternative to attain a therapeutic effect against infections or inflammations. Several trials have demonstrated the benefit of functional foods in various pediatric diseases and in the management of specific gastrointestinal conditions. These include acute infectious diarrhea, antibiotic-associated diarrhea (*Clostridium difficile* associated or not), *Helicobacter pylori* gastritis, food allergy, lactose intolerance, necrotizing enterocolitis (NEC) and inflammatory bowel disease (IBD). According to the report of the Working Group on Functional Foods and Probiotics of the World Congress for Pediatric Gastroenterology, Hepatology and Nutrition (Boston, August 2000), pro/prebiotics have been shown 1/ to have effects in some diseases (lactose malabsorption, acute viral enteritis, antibiotic associated diarrhea and atopic dermatitis), 2/ to have positive (*Clostridium difficile*, NEC, acute respiratory illness) or promising effects (IBD and NEC) in some others, 3/ to sometimes produce mixed results (H. *pylori* and travelers diarrhea), and 4/ to have potential applications in a series of situations (vaccine booster, cancer prevention, constipation and hypercholesterolemia).

One of the most obvious indications for the use of probiotics is the treatment or prevention of diarrhea. Table 2 gives an overview of numerous studies using probiotics in pediatric populations with diarrhea. The table is subdivided according to the probiotic. The wide variety of microorganisms involved and the different populations studied preclude blanket recommendations. Among the best demonstrated effects yet are those of the use of *Lactobacillus GG* and *Bifidobacteria*. Other *Lactobacilli* and the yeast *Saccharomyces boulardii* also have been investigated, with positive outcomes. Results of the trials show a decreased duration, severity and incidence of diarrhea. The use of *Lactobacillus acidophilus* in studies with preterm infants had no effect. Another study demonstrated that a combined supplementation of probiotic bacteria, *Lactobacillus rhamnosus*, prebiotic (dietary fiber) and micronutrients could reduce the duration of acute diarrhea of infants in developing countries (40).

In a recently published multicenter study, the efficacy of *Lactobacillus GG* was assessed in combination with oral rehydration solution (ORS). *Lactobacillus GG* was found to be safe and resulted in shorter duration of diarrhea, less risk of a protracted course and faster discharge from the hospital (41). Probiotics also have an effect on intestinal allergy. Addition of *Lactobacillus GG* to a hydrolyzed whey formula has been demonstrated by

Table 2. — **Studies with probiotics in pediatric populations with diarrhea**

Author	Study population	Pro/prebiotic	Clinical Outcome
Isolauri *et al.*, 1991 Kaila *et al.*, 1992 Raza *et al.*, 1995 Pant *et al.*, 1996 Shornikova *et al.*, 1997 Rautanen *et al.*, 1998	71 children 39 children 40 children 39 children 123 children 30 children	Lactobacillus GG	Decreased duration of infectious diarrhea
Biller *et al.*, 1995 Young *et al.*, 1998	4 children 188 children	Lactobacillus GG	Less severe AB-associated diarrhea
Pedone *et al.*, 1999	287 children	Lactobacillus casei	↓ severity diarrhea
Reuman *et al.*, 1986 Millar *et al.*, 1993	20 preterm infants 30 preterm infants	Lactobacillus acidophilus	No effect No effect
Chapoy *et al.*, 1985 Cetina-Sauri *et al.*, 1989 Buts *et al.*, 1993	38 children 130 children 19 inf with Cl diff enteropathy	Saccharomyces boulardii	↓ transit time ↓ stool frequency ↓ stool weight
Fukushima *et al.*, 1997	7 children	Bifidobacterium bifidum	↑ Bifidobacteria ↓ Clostridia
Saavedra *et al.*, 1994	55 infants	Bifidob. bifidum + Strept. thermophilus	↓ incidence of diarrhea

References (35,53-67).

Table 3. — **Animal studies applying pro- or prebiotics in populations with NEC**

Author	Study population	Pro/prebiotic	Clinical Outcome
Butel *et al.*, 1998 (68)	Quails	Bifidobacteria strain	Suppression of all pathological lesions
Catala *et al.*, 1999 (69)	Quails	Oligofructose	↑ Bifidobacteria ↓ E Coli ↓ Clostridia
Caplan *et al.*, 1999 (70)	Rats	Bifidobacteria infantis	↓ incidence of NEC

Majamaa to result in a significant improvement of a clinical allergy score (42). The beneficial effects in allergy have been attributed to the ability of probiotics to promote the non-immunological defense barrier in the gut, normalization of intestinal permeability and normalization of unbalanced flora in inflammation.

NEC is a life-threatening intestinal disease primarily affecting premature neonates. The clinical manifestations include abdominal distension, rectal bleeding and ultimately intestinal perforation (43). The pathogenesis is multifactorial resulting from gut immaturity and action of intestinal bacteria. The bacteria isolated from affected infants are normal members of the neonatal gut flora, most commonly *Klebsiellae* (44), *E. coli* (45) and *Clostridiae* (46,47). Among *Clostridia*, the most frequently isolated species are *C. butyricum* (48) and *C. perfringens* (46,47). Three studies using animals inoculated with preterm infants' flora demonstrated a suppression of pathological lesions after adding a probiotic strain or a prebiotic (table 3). These studies indicate that pro- and prebiotics may help prevent NEC. Hoyos *et al.* also demonstrated that daily administration of *Lactobacillus acidophilus* and *Bifidobacterium infantis* is effective in decreasing NEC occurrence in newborn infants admitted in intensive care units (49).

Probiotics were also applied in irritable bowel syndrome. A study in children with chronic, recurrent abdominal pain showed a slight, but statistically significant reduction in severity of abdominal pain. The probiotic used in this study was *Lactobacillus plantarum*, which is known to synthesize nitric oxide — an important mediator of gut motility (50).

An area of great potential interest is that of inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis. Theoretical considerations suggest a role for bacteria in the initiation of IBD and therefore probiotics probably can interfere with this abnormal inflammatory response. It is likely that *Lactobacilli* could result in decreased inflammation by preventing the growth of pathogenic bacteria and by maintaining the integrity of the gut barrier (51).

Since children attending day-care centers have a higher incidence of both gastrointestinal and respiratory infections than those taken care in small groups, a study with *Lactobacillus rhamnosus GG* was performed in a group of 252 children aged 1-6 years. Results showed that the rate of gastrointestinal and respiratory symptoms during a period of 7 months was reduced by 4 to 11% (52).

Conclusion

The concept of functional foods has evolved together with a changing attitude towards nutrition. Functional foods provide a unique opportunity to contribute to the improvement in health and the prevention of infant diseases. The most novel and interesting category are the pro- and prebiotics. Various (infant) feedings or feeding supplements with pro- or prebiotics are commercialized now. The beneficial role of pro- or prebiotic functional foods in infants have already been demonstrated. Unequivocal evidence exists that probiotics are useful in viral diarrhea illnesses and allergic diseases. They might also be important in the treatment and prevention of a number of inflammatory disorders. Besides pediatric gastrointestinal disorders, functional foods also find an application in daycare situations.

A collaboration of various disciplines, such as pediatric gastroenterology, nutrition, microbiology and immunology is essential to ensure that the full potential of functional foods in infant nutrition is achieved.

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