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Functional Foods

Developments in colonic functional foods for improved digestive health

Functional foods

The food industry has recently shown greatly increased interest in the concept of “functional foods” and such products are proliferating rapidly in health food stores and supermarkets across Europe. Of course, all food can be seen functional in that it generates nutrition and energy. A functional food, however, is one which provides a specific health benefit over and above its normal nutritional status [1]. Examples include juices and beverages fortified with calcium or other minerals, spreads containing phytosterols that prevent cholesterol absorption from the gut and vitamin additions.

Of the various functional food categories, the most rapidly developing and promising are those for improving gastrointestinal (GI) health. These interact with and modify the complex microbial ecosystem resident in the gut with the aim of reducing disease risk.

The GI tract microflora

The GI tract runs from mouth to anus and is variably colonised by micro-organisms, predominantly bacteria, throughout its entirety [2]. Bacterial populations are around 10^5 cells/ml in the mouth (although much higher in plaque), falling to about 10^3 in the stomach before rising to 10^4 - 10^6 cells/ml in the small intestine. The colon, however, is by far the most heavily colonised region in the human body with around 10^{12} cells/ml. This huge bacterial load amounts to about 1kg of bacteria, forming 20 times more microbial than human cells in the body. This number exceeds total people who have lived on the planet and each one of us is reckoned to excrete the equivalent weight of 12 elephants in faecal bacteria during our lifetimes! The strictly anaerobic bacterial community in the colon is very complex and it is estimated that we have yet to uncover around 50% of the biodiversity present, although those which are most functionally relevant have been described.

It is therefore apparent that the colon is an extremely metabolically active organ which has a major impact on human health. Apart from chronic gut disorders such as ulcerative colitis, Crohn's disease and irritable bowel syndrome (IBS) which cause misery to many people, colon cancer is the second biggest cancer killer in

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Europe. Moreover, the vast majority of us suffer at some time or another with an acute GI infection, which is generally food-borne. GI problems take up more clinical time than all other complaints added together. Most are believed to have a microbial involvement at some point in their development [3, 4, 5]. It is known, for instance that certain members of the gut flora produce powerful toxins and carcinogens. Sulphate reducing bacteria, which produce highly toxic H₂S have been implicated in ulcerative colitis, whilst the carriage of *Candida* yeasts may be involved in IBS. Other members of the ecosystem such as species of the genera *Bifidobacterium* and *Lactobacillus* are entirely benign in their activities, producing beneficial compounds from carbohydrate metabolism (Fig. 1). Such species also help to protect us from invasion by pathogens by competing for nutrients and cellular receptors, improving the immune response and producing anti-microbial compounds [6].

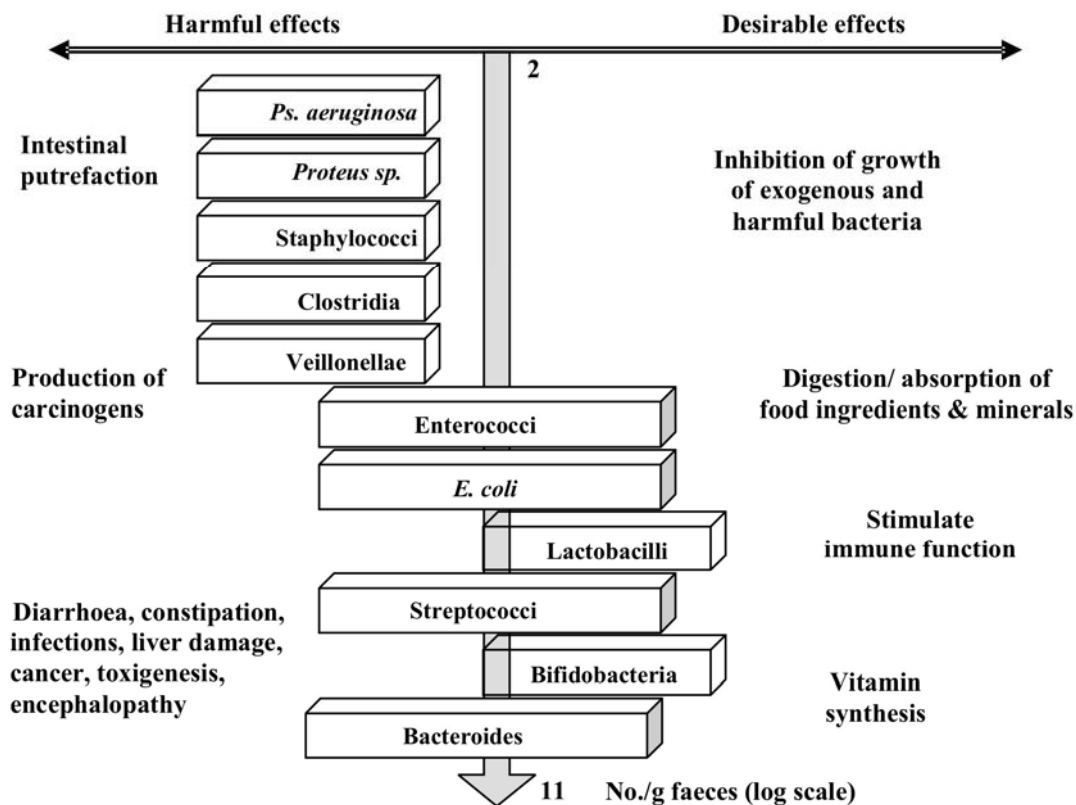


Figure 1. A simplified view of the colonic ecosystem. Bacterial groups to the left of the bar are predominantly negative in their effects on human health whilst those to the right are beneficial. Some groups are on both sides of the bar, these contain both beneficial and harmful species.

Probiotics

It has long been recognised that there is huge potential in manipulating the GI ecosystem via the diet. Traditionally this has been attempted by the use of probiotics. A probiotic is defined as “A live microbial supplement, which beneficially affects the host animal by improving its intestinal microbial balance” [7]. They have a long history of use beginning with the work of Eli Metchnikoff at the turn of the last century, who studied the effects of so called “soured milks” upon longevity in Bulgarian peasants. A range of health benefits have been claimed for probiotics (Table 1) although in some

Table 1. Postulated health benefits of probiotics.

Assist in digestion of lactose in lactose intolerant individuals
Stimulation of immunity
Increased resistance to pathogens e.g. traveller's diarrhoeae
Decrease risk of colon cancer
Alleviate atopic eczema
Alleviate cow's milk allergy
Regularise gut microflora after antibiotic therapy

cases the mechanisms behind these effects have not been fully elucidated. The best understood of these is inhibition of invading pathogens like campylobacters, salmonellae, *E. coli*, etc. Many probiotics produce powerful anti-

microbial agents, which are active against many aetiological factors of gastrointestinal distress [6]. There have been many studies on the health benefits of probiotic intake over the years. These have unfortunately been of somewhat variable quality and have therefore given equivocal results in many cases [8].

Most of the probiotics incorporated into food products (generally dairy products) are species of *Lactobacillus* (Table 2). This is primarily due to technical reasons, as lactobacilli are facultative anaerobes and can tolerate exposure to oxygen during food formulation, transport and storage. In terms of biological activity, however, *Bifidobacterium* species may be a preferred choice in that they generally produce more potent anti-microbial activities. As these species are obligate anaerobes, however, they are more difficult to incorporate into food products [9].

Table 2. Some representative commercial probiotic species

<i>Lactobacillus acidophilus</i>
<i>Lactobacillus reuteri</i>
<i>Lactobacillus plantarum</i>
<i>Lactobacillus casei</i>
<i>Lactobacillus johnsonii</i>
<i>Lactobacillus rhamnosus</i>
<i>Lactobacillus gasseri</i>
<i>Bifidobacterium lactis</i>
<i>Bifidobacterium infantis</i>
<i>Bifidobacterium longum</i>

There is currently much development research ongoing in the area of probiotics [10]. One of the most significant is the targeting of probiotic strains at specific disease conditions. With the increasing problems of antibiotic resistance and its widespread use, the idea of using probiotics to combat specific medical complaints rather than to boost well-being is receiving renewed attention. Probiotic candidates can be screened specifically for their anti-microbial activities against specific pathogens, survival properties in the gut and developed for application in specific disease states. Another area of interest is the idea of developing specific probiotics for application in certain target populations. In this context, there is currently a large EU collaboration aimed at identifying novel probiotics and synbiotics (see below) aimed at maintaining/restoring gut health in the elderly [11].

Whilst probiotics have a long history of technological development, there are some concerns over their efficacy. The obstacles to successful persistence of ingested probiotics are considerable. Firstly, there is the food manufacturing process itself and a subsequent refrigerated storage and distribution process. After consumption, the bacteria must survive passage through the stomach at pH 1-3 then through the small intestine where they will be exposed to toxic bile compounds and pancreatic enzymes. Upon reaching the colon, the ingested bacteria must successfully compete with the huge numbers of resident bacteria. It is unlikely that all of the probiotic strains currently in commercial use can

achieve this, although some products do use protective delivery systems such as micro-encapsulation.

Prebiotics

The concept of prebiotics is relatively new. A prebiotic is defined as “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 that can improve the host health” [12]. All current prebiotics are non-digestible oligosaccharides. A prebiotic therefore aims to selectively feed probiotics indigenous to the human colon. Hence, the health benefits of prebiotics are largely similar to those of probiotics. One big advantage with prebiotics, however is that they are non-viable food ingredients. This provides the food manufacturer with far more flexibility with respect to the products that can be made. Prebiotics can, for instance, be formulated into baked goods such as biscuits – heat processing that no probiotic could ever survive!

Table 3. Commercially available prebiotic oligosaccharides

Lactulose
Galacto-oligosaccharides
Fructo-oligosaccharides
Isomalto-oligosaccharides
Soybean oligosaccharides
Lactosucrose
Xylo-oligosaccharides
Gentio-oligosaccharides

There is a range of recognised prebiotics on the market internationally (Table 3), with the greatest range currently available in Japan [13]. The market leaders in Europe are the fructose-containing fructo-oligosaccharides (FOS) and the polysaccharide inulin. FOS are either manufactured from inulin by enzymatic hydrolysis or by enzymatic transfer reactions from sucrose. Other major prebiotics in Europe are the galacto-oligosaccharides. These are produced from lactose (a significant, problematic, waste material from the dairy industry) by transfer reactions catalysed by β -galactosidase.

There are a range of health benefits that have been claimed for prebiotics, most of which are in common with probiotics (Table 4). As with probiotics, in many cases we have no clear understanding of the mechanisms behind these effects.

Table 4. Postulated health benefits of prebiotics

Stimulation of immunity
Increased resistance to pathogens e.g. traveller’s diarrhoea, food poisoning
Decrease risk of colon cancer
Stimulate calcium absorption from the colon
Potentiate effects of probiotics

The science supporting the prebiotic concept is developing rapidly. Most of the readily avail-

able carbohydrate resources are being systematically investigated for their prebiotic properties or for their capacity to become prebiotic upon enzymatic modification. It is very likely that we will see several novel forms emerge on the market in the coming years [14]. There are specific targets to this prebiotic development exercise, however. Principal among these is the development of prebiotics that persist throughout the length of the colon. Most of the more chronic disorders such as ulcerative colitis and colon cancer originate in the distal

region of the colon, which tends to be very proteolytic in its microbial metabolism. Protein fermentation by gut bacteria generates high levels of toxins and tumour promoters. Prebiotic carbohydrates that are fermented in this region might therefore be expected to reduce this toxic load and alleviate the incidence of colon cancer. Furthermore, butyric acid, one of the products of carbohydrate metabolism by colonic bacteria, is believed to be protective against colon cancer through its ability to stimulate apoptosis (programmed cell death). Other targets for development work include prebiotics that are very selectively fermented by probiotics, rather than by the bacteria that produce hydrogen as a metabolic end product. Intestinal gas production is a well-documented and embarrassing side effect of excessive consumption of some prebiotics. A more targeted fermentation by the probiotics will alleviate this problem and provide prebiotics that are active at very low concentrations.

Synbiotics

Building upon the concepts of probiotics and of prebiotics, a synbiotic is defined as "a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplement in the GI tract" [12]. The aim is to improve survival prospects of a probiotic that has well-defined health benefits by formulating it with a prebiotic that it can readily metabolise in the competitive gut ecosystem [15]. Synbiotic products are beginning to appear on European supermarket shelves. Generally these exploit FOS or inulin together with probiotic *Lactobacillus* or *Bifidobacterium* species. An exciting possibility is to search for prebiotics that are preferentially utilised by the particular species of probiotic to be used. This would then give the probiotic a selective advantage over those that are indigenous. Recent developments in carbohydrate biotechnology allow the production of oligosaccharides using enzymes isolated from the probiotic itself.

Future perspectives

The future is extremely promising for dietary modulation of the colonic microflora to promote health. The colonic ecosystem is extremely complex and we have an imperfect understanding of the activities of much of the resident microflora and their ecological interactions. This situation is being remedied through the application of powerful new molecular biological tools for studying such complex microbial communities [16]. The identification of bacteria can now be performed routinely using reliable molecular tools such as hybridisation of DNA probes to the 16S rRNA genes. These genes contain specific diagnostic regions, unique to each genus, species and even strain of bacteria. The information in

these genes can also be used in genetic fingerprinting techniques to study biodiversity of the colonic ecosystem and the levels of expression of bacterial genes can give clues as to the metabolic activities of members of the community. Such studies will undoubtedly lead to new probiotics as well as a clearer understanding of the health benefits they can derive.

Many probiotic genomes are currently being sequenced [17] and it is certain that this information will facilitate the development of “designer probiotics” with desirable traits to equip them for improved functionality. Commercialisation of such organisms is likely to be some way in the future, but development of engineered strains in the laboratory will allow us to obtain the mechanistic understanding of probiotic and prebiotic action that is currently lacking.

It is also clear that as we gain a further understanding of the variation in colonic biodiversity within individuals and within groups, we can look forward to dietary intervention tools targeted in a much more rational way than is achievable at present.

Functional foods: Foods that have a specific health benefit beyond nutrition such as improvement of gut health, reduction in cholesterol, etc.

Probiotic: Live bacteria eaten as part of a food product. They are health-promoting species such as *Lactobacillus* spp. and *Bifidobacterium* spp. that are found in the human colon.

Prebiotic: A carbohydrate, non-digestible by humans, that *selectively* feeds the indigenous probiotics in the human colon.

Synbiotic: A combination of a probiotic and a prebiotic.

The uptake of probiotics, prebiotics and synbiotics has varied from country to country with some, notably the UK, lagging behind. If these dietary management tools are to have a significant impact on public health then it is imperative that consumers are more fully educated about the function of the colonic microflora and its role in maintenance of health. This needs to be followed by commercialisation based upon rigorously proven science to bolster confidence on the part of consumers and health-care professionals.

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Keywords:

Functional foods, probiotics, prebiotics, synbiotics, gut health