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Viewpoint

Probiotics: how should they be defined?

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Probiotics have been defined in several ways, depending on our understanding of the mechanisms of action of their effects on health and well-being of humans. The term probiotic was coined by Lilly and Stillwell [1] to describe substances produced by one microorganism, that stimulate the growth of another, thus meaning the opposite of antibiotics. Parker [2] subsequently defined probiotics as organisms and substances that contribute to intestinal balance. This definition, however, did not exclude antibiotics. At present, the most commonly used definition is that of Fuller [3]: *Probiotics are live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance*. Recently a European expert group widened the definition to include mechanisms other than just microflora mediated ones. The definition was as follows: Probiotics are live microbial food ingredients that have a beneficial effect on human health [4,5].

To include the current application and scientific data on proven effects of probiotics we propose the following definition: *Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host*. This definition implies that probiotics do not necessarily need to be viable. Non-viable forms of probiotics have also been shown to have health effects [6]. The definition does not restrict the use of probiotics in foods; several other applications have been reported to have beneficial health effects. Not only whole microbial cells, but also parts of cells have been observed to improve host health. Metabolites are, however, not included in the current definition. Thus, it excludes antibiotics. The proposed definition is based on the mechanisms of action, selection criteria, viability and non-viability, and scientifically documented health effects that will be discussed.

Mechanisms of action of probiotics

The mechanistic approach to probiotics first established that many gastrointestinal dysfunctions are based on disturbances or imbalances of intestinal microflora. Thus, probiotics were defined as viable microbial cultures that influence the health of the host by balancing the intestinal microflora and thus preventing and correcting the microbial dysfunctions. This still applies to many probiotic studies and has been verified with many specific viable cultures [4,5] and non-viable cultures [6]. Examples of the proposed mechanisms of probiotics in humans are summarized in Fig. 1.

Safety

Safety is an important requirement for probiotics. All microbes can be classified in terms of their relative safety and divided into three groups: (1) nonpathogenic, (2) opportunistic pathogens, and (3) pathogens. Every viable microbe that is able to grow under the conditions encountered in a host, can cause an infection under certain circumstances (e.g. in severely immunocompromized hosts). The likelihood of any food or normal intestinal microbe causing an infection in the host is relatively small. Most intestinal microorganisms are not pathogenic in healthy individuals. These microbes result in a symbiosis between the host and the microbe and the development of such symbiotic microflora may be governed by inoculation from the mother, genetic background and even the method of birth. Some intestinal bacteria are potentially pathogenic and their growth and metabolism is influenced by the normal immune system in the digestive tract. The third group, pathogenic microbes, is the smallest of the three classes and they can potentially cause an infection even in a healthy host. Non-viable or inactivated microbial preparations

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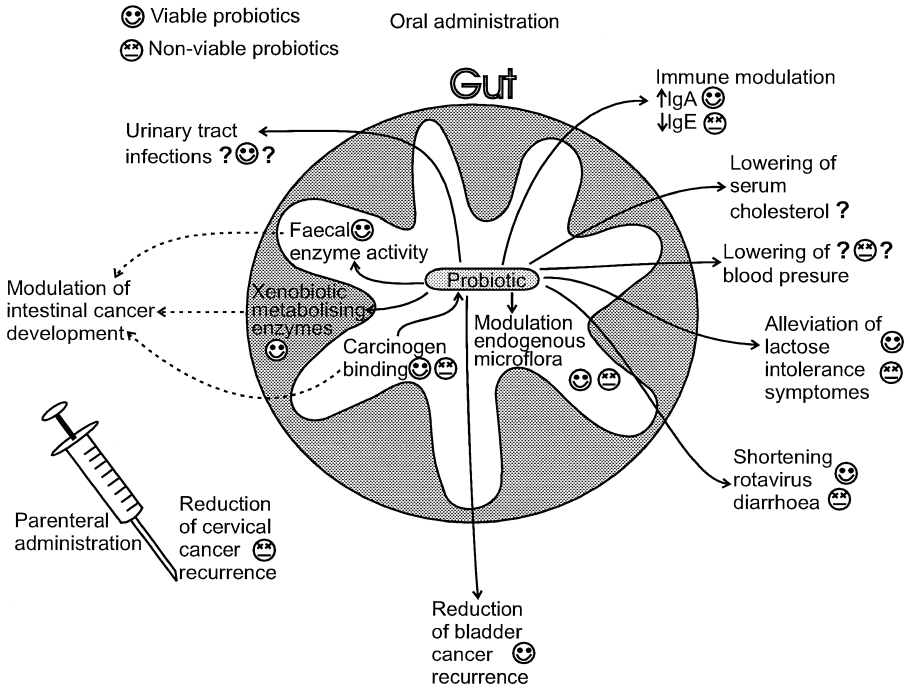

Fig. 1. Proposed mechanisms of viable and non-viable probiotic health effects.

have very few, if any, adverse effects. There is a possibility of adverse reactions to the protein components but such reactions have not been reported for currently used probiotics, viable, non-viable or cell wall components (Table 1). Even though current probiotics are considered safe for food use [6–9], non-viable probiotics and microbial cell wall components are the least likely to cause safety concerns.

The scientifically proven health effects of probiotics were recently reviewed by an ILSI Europe working group on functional foods [4,5]. Specific strains were reported to have several well documented health effects that could be backed by scientific studies and proven hypothesis. These effects have been documented for specific viable probiotics (Table 2).

Health effects of non-viable probiotics

Health effects of non-viable probiotics have been recently summarized by Ouwehand and Salminen [6]. It is clear that non-viable probiotics have some documented health effects, too. Recent studies have also shown that effects on human health and well-being do not necessarily involve changes in the intestinal microflora or viability of the probiotic [4–6,10]. These studies have indicated that viability is not necessary for all probiotic effects, but further studies comparing viable strains and products with non-viable strains are urgently needed. In addition, recent studies involving not only heat-killed or otherwise inactivated microbes have shown that even the cell wall components on some probiotic microbes may have significant effects of the

Table 1. Risks and benefits of viable versus non-viable (including bacterial cell wall preparations) probiotics

Preparation	Benefits	Risks	Questions
Viable	Best documented health effects	Transfer of antibiotic resistance Limited shelf-life May be extremely rare causes of allergenicity infection?	Dose–response Virulence factors? How to preserve viability?
Non-viable	Documented health effects No risk of infection Excellent shelf-life No transfer of antibiotic resistance	Allergenicity	Dose–response Allergenicity?
Cell-wall component	Some documented health effects No risk of infection Excellent shelf-life No transfer of antibiotic resistance	Allergenicity?	Allergenicity? Better dose–response effect

Table 2. Established health effects of probiotics [4,5]

Scientifically established	Alleviation of symptoms of lactose intolerance
	Immune modulation
	Shortening of the duration of rotavirus diarrhoea
	Decreasing faecal mutagenicity
	Decreasing faecal bacterial enzyme activity
	Prevention of recurrence of superficial bladder cancer

health and well being of humans when incorporated into the diet. However, clear well-designed studies comparing viable to non-viable probiotics have not been conducted. Thus, there is an urgent need for support for such studies. Until these studies have been conducted it is impossible to judge whether viable probiotics are superior to non-viable ones.

Probiotics as biotherapeutic agents or ingredients for functional foods?

As proposed in the functional food science in Europe project [4,11] it is important that all research on health effects is science, hypothesis and evidence based, and documented in well-planned nutritional and clinical studies in humans. Knowledge of the mechanism(s) by which probiotics can modulate target function(s) and their relevance to the state of well-being and health and/or reduction of a disease will originate from basic knowledge in the biological sciences. It may also be supported by epidemiological data, which could demonstrate a statistically validated relationship between the intake of individually specified probiotics (viable, non-viable or component of the microbe) and the specific benefit. It will be of particular value to have good prospective evidence that links the habitual intake of a specified probiotic component with subsequent disease risk.

Research needs

Some urgent research needs are described in Table 3. In general, the differences between viable and non-viable probiotics should be carefuly assessed in *in-vitro* studies and especially in human studies. It is important to understand the correlation between the consumption of foods with such microbes and the healthy intestinal microflora. More methods need to be developed to characterize intestinal microflora, including the non-culturable species. Molecular approaches based on the separation and identification of genetic material, such as 16S ribosomal RNA, are promising and the presence of viable and non-viable components as well as the influence of bacterial destruction and the release of bacterial DNA in the gut. We particularly need to understand the role of the diet and probiotics, viable or non-viable or cell wall components in the general modulation of immune functions, specifically the exact role of gut-associated lymphoid tissue (GALT).

Markers related to immune functions associated specifically with GALT need to be developed and validated, since stimulation of the immune system may not necessarily require affects on the indigenous microflora. Also, probiotics may (but not necessarily) change the immune response in healthy subjects and there are a few reports for some specific strains [12–14].

Improved characterization and validation of the composition of bacterial genera species and strains and the activities of the colonic microflora (e.g. specific enzymes, carcinogen formation is needed). Similarly, the composition of viable and non-viable components in the gut needs to be established. Further well designed trials to examine the effects of different probiotics whether viable or non-viable, or cell wall components are urgently needed.

The long-term effects of permanent changes in the composition of the colonic microflora need to be monitored. Similarly, few data on the long-term effects of probiotics are available concerning influences on intestinal microflora or other target functions in humans.

Conclusions

In conclusion, a new definition for probiotics may better characterize both the specific strains and components used for probiotic purposes. It would also require specific clinical documentation in human subjects to back any health effects and health messages. Thus, we propose that *Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host*. This definition implies that probiotics do not necessarily need to be viable as non-viable forms of probiotics have also been shown to have health effects. The definition neither implies that probiotics have to be used only in foods; several other applications have also been found to have beneficial health effects.

Table 3. Urgent research needs for probiotics [4–7,9,11]

Research need	Importance of viability
Effects of probiotics on normal intestinal microflora	Do non-viable probiotics have effects on intestinal flora
Immune effects of probiotics in normal subjects and subjects with gastrointestinal disease	Do non-viable probiotics have immune effects in humans
Probiotic effects on intestinal metabolism	Effect of non-viable probiotics on intestinal metabolism
Demonstration of health effects in human studies	Effect of viability on health effects

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