The (non-) sense of human origin of probiotics

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ABSTRACT

One of the selection criteria for probiotics for human use is 'human origin'. In addition to the problem of how to define human origin, there does not seem to be evidence to substantiate this requirement. Probiotics from non-human origin have been shown to provide health benefits in humans and while those of 'human origin' have been found to provide health benefits in animals. Instead, safety and efficacy of probiotics seem to more relevant focus areas.

INTRODUCTION

Probiotics have been defined in many ways. Currently the most commonly accepted definition is the one suggested by a working group of the FAO/WHO: "probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host" (1). Although this and other definitions tell us what probiotics are, they do not tell us what specific properties probiotics should possess (if any).

Many authors have suggested lists of selection criteria or properties thought to be necessary for successful probiotics. There appears to be a general agreement on the need for certain properties of probiotics, such as resistance to environmental stresses (e.g. acid and bile) during gut transit and during the manufacture and storage of probiotic products, safety (especially absence of transferable antibiotic resistance), and documented health benefits (2-9) (Table I). Furthermore, there is the suggestion that when probiotics are intended for human use, human origin of the strains is also an important selection criterion (3,4). Here, we will discuss the pro's and con's of this suggested selection criterion.

Table I – Suggested selection criteria for probiotics
Compiled from Refs. 3,4,18

Property	Comment
Acid resistance	Survive gastric passage
Bile resistance	Survive small intestinal passage
Resistance to digestive enzymes	Survive gastrointestinal passage
Adhesion to intestinal mucosa	Though to improve transient colonisation Provide resistance to incoming pathogens Better interaction with the immune system
Safe	Accurate taxonomic identification Absence of transferable antibiotic resistance
Technological suitability	Can be mass produced Is genetically stable Stable in product Suitable for consumer product
Validated health effects	Health benefits have to be substantiated
Human origin	Suggested host specificity

HOST SPECIFICITY OF PROBIOTICS, THE SENSE OF HUMAN ORIGIN

By the current definition, probiotics need to be viable. Although non-viable 'probiotics' do not always seem to be without health effects, studies that have compared viable and non-viable 'probiotics' are scarce, and in general it is thought that that live probiotics are superior (10). Furthermore, there is the common assumption that probiotics need to remain viable in the intestine in order to be efficacious, despite that much of the research on the mechanisms of the probiotic function (e.g. modulation of immune responses) is in fact based on studies with non-viable probiotics.

The intestine is a very specific environment, which places incoming microbes for many challenges such as low pH, digestive enzymes and bile. Resistance to these stresses are therefore common selection criteria. Living organisms in general, and microbes are no exception to that, are well adapted to their natural environment. It is

therefore reasonable to look for probiotic candidates among the microbes in the intestine or from faeces. There are substantial differences between different animal species in intestinal anatomy, physiology (11) and microbiota (12). Therefore, it seems reasonable to select potential probiotics from the same host species as they are intended to be consumed by. Hence, probiotics for humans would need to be of human intestinal/faecal origin. However, this approach places us for a number of challenges which will be discussed below.

WHO WAS HERE FIRST ANYWAY?

The first objection to the idea is purely philosophical; human origin of microbes is clearly not possible. Microbes were present on Earth long before human emerged. Also many of the species that are part of the 'normal' human intestinal microbiota are present in other mammalian species and are therefore likely to have evolved independent of humans. Microbes, and thereby also probiotics, do not originate from humans.

WHAT HUMAN ORIGIN?

More relevant is the question how to prove that a probiotic was isolated from a human and that it was actually a long standing member of the human intestinal microbiota.

As proof for human origin it is often thought to be sufficient that the strain was isolated from human faeces. However, this merely indicates that the isolated microbe has been able to survive passage through (part of) the gastro-intestinal tract. Although this is considered another probiotic selection criterion, it does not prove that the microbe is a permanent member of the human gastro-intestinal microbiota. Even less so, it indicates whether the isolate is a potential probiotic.

As an example, it can be mentioned that people with a high consumption of Emmental cheese tend to have high levels of propionic acid bacteria in their faeces. These propionic acid bacteria are typical starter cultures for Emmental cheese. But, the fact that they can be reisolated from the faeces of the consumer does obviously not make them there after of human origin.

It should be also noted that the microbiota composition of humans varies between subjects and also during the life time of a subject. Furthermore, there appear to be geographic differences in the intestinal microbiota of subjects (13). Thus, strains that are naturally present in the microbiota of one subject are possibly not present in most other subjects. Therefore, a *Lactobacillus* strain which may be specific for the subject from whom it was isolated from may be 'foreign' to other human subjects, in a similar way as any other *Lactobacillus* strain isolated from animals or dairy products.

HOST SPECIFICITY OF HEALTH EFFECTS – DOES IT EXIST?

As mentioned above, the reason to select for probiotics from e.g. human gastrointestinal contents or faeces is the assumption that there is host specificity for microbes. There are differences in the microbiota composition of different animal species (12). Although the same species may be identified, they are often present at different levels or at different anatomical sites. Furthermore, many pathogens have a high degree of host specificity and either do not survive in another host or do not cause disease (although of course zoonoses exist). These observations would indicate at least a certain level of host specificity among members of the intestinal microbiota and therefore also possibly among probiotics.

A considerable number of probiotic strains have been isolated and are being marketed for human use. Some of these strains have also been tested in animals, for various reasons. On one hand, animals and in particular rodents are used as experimental animals. It is clear from the literature that probiotics intended for human use also have health effects on animals. As an example, *Bifidobacterium lactis* HN019 and *Lactobacillus rhamnosus* HN001 have first been shown in animals to modulate the immune system (14) and subsequently, this has been confirmed in humans (15). Furthermore, the strains were shown to reduce severity of weanling diarrhoea caused by *E. coli* and rotavirus (1). The latter is actually also a major cause of diarrhoea in infants. Similar examples exist for many other probiotic strains. In fact, the assumption of an absence of host specificity forms a basic rationale for animal experiments.

Also in other settings it has been shown that probiotics for human use can provide health benefits in animals. *Lactobacillus rhamnosus* GG has been shown to improve the survival of rainbow trout from furunculosis (17).

MECHANISMS OF PROBIOTIC FUNCTION AND HOST-SPECIFICITY

Host specificity has been argued to play a role in the colonization of probiotics in human intestine, a proposed mechanism for probiotic function. However, current evidence suggests that orally consumed probiotic bacteria do not colonize the consumer permanently. Colonization is temporary at best, and usually the possible health effects take place only during the administration of probiotics (15). It should be remembered that a strain that is isolated from a certain human subject is 'part of natural intestinal microbiota' of that person, but the same strain is 'foreign' strain to most other people. This may be the reason why a strain isolated from certain person is unlikely to colonize in other persons.

Another proposed mechanism of probiotic action is the modulation of immune function. Probiotics may exert their health benefits e.g. by up-regulating the immune response against pathogens or down-regulating the immune responses in hypersensitive subjects. The ability of probiotics to modulate the immune function may be due to the fact that they are 'foreign' (albeit safe) microbes to the host. This may be especially true in the case of up-regulation of host immunity. The immune system detects probiotics as foreign microbes and responds by 'priming up' the defence systems, thereby enhancing the defence against pathogenic bacteria. In this case it does not make a difference whether the probiotics used are of 'human origin' or not; it is more important that the microbes are safe to use and that they are capable of inducing immune responses.

SAFETY OF PROBIOTICS OF NON-HUMAN ORIGIN

One of the arguments for using human origin as a selection criterion for probiotics is the safety of the strains: it is assumed that probiotic strains isolated from humans are more likely to be safe for human consumption than strains isolated from other sources. However, 'human origin' is by no means a guarantee for safety. Many intestinal microbes commonly harboured by humans, such as certain strains of *Clostridium* and *Staphylococcus*, may have pathogenic potential. The genetic identity and the physiological properties of the candidate probiotics determine the safety of the strains. For example, strains of *Bifidobacterium* can be generally considered as safe for human consumption, regardless of the host from which the strain has been isolated from.

EXAMPLES OF PROBIOTICS THAT ARE NOT OF HUMAN ORIGIN

Probiotics intended for humans appear to have health effects on animals. But,

examples do also exist for probiotic strains that were not isolated humans but have health benefits in humans nevertheless. Several well-documented probiotic strains that are of dairy origin may therefore originate from the dairying process or from the lactating animal. These include *Bifidobacterium lactis* Bb-12, *B. lactis* HN019 and *Lactobacillus rhamnosus* HN001. Furthermore, probiotic yeast *Saccharomyces cerevisiae* (*boulardii*) was isolated from lychee leaves in south-East Asia. The success and the documented health effects of these probiotic strains demonstrate that to be beneficial for humans, probiotic strains do not have to be of 'human origin'.

CONCLUSION

Current knowledge does not support the idea that probiotics for human use need to be of human origin, apart from the difficulties in proving that the strain is actually an isolate of a member of the normal intestinal microbiota. The origin, as long as it is not from diseased tissue, does not seem to be of major relevance. Instead, safety and documented efficacy should be the main points of focus.

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