

Health Benefits Mediated by Probiotics - How Can we Better Establish Them?

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Various probiotic as well as prebiotic and synbiotic products have already been and continue to be developed with the rationale of shaping the gut microbiota towards a more beneficial composition. Probiotics have been defined as “Live organisms which when administered in adequate amounts confer a health benefit to the host” (FAO/WHO 2001 joint report: http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf). However, without having a clear understanding of what the actual benefits of such microbiota directed products are it is nearly impossible to even start exploiting their expected positive impact on public health.

Current regulatory concerns appropriately limit the health claims that can be made regarding benefits associated with any commercially available probiotic supplement. Clearly, customers need to have the means for protecting themselves from unsubstantiated health benefit claims. The US FDA broadly categorizes health benefit claims on food labels as either: 1) Health claims, 2) Structure/function claims, or 3) Nutrient content claims. FDA also considers qualified health claims that contain a disclaimer summarizing current research support for the claim. FDA defines dietary supplements as “a product intended for ingestion that contains a ‘dietary ingredient’ intended to add further nutritional value to (supplement) the diet. A ‘dietary ingredient’ may be one, or any combination, of the following substances: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by people to supplement the diet by increasing the total dietary intake, a concentrate, metabolite, constituent, or extract” (<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm195635.htm>).

It is not obvious how well probiotics fit the above description of dietary supplements. Probiotics can provide a variety of functions otherwise not available to the human host, including enzymatic activities uniquely capable of efficiently metabolizing complex compounds such as dietary fibers, mucins, bile acids etc. There are many mechanisms, including generation of short term fatty acids (SCFA) and interactions with host immune system, that have been suggested as beneficial functions of probiotics [1-3]. However, such functions might already be provided in ‘nutritionally sufficient’ amounts by an individual’s commensal gut microbiota. It remains to be defined what exactly ‘nutritionally sufficient’ amounts of such microbial enzymatic activities and other functions or ‘adequate amounts’ of probiotics are.

Current regulations limit how probiotics’ health benefits can be effectively studied in humans. Requirements for adhering to strict regulations necessary to protect individuals from exposure to the potential side effects of novel drugs often make probiotic studies that are aimed at providing evidence for specific health benefits cost prohibitive. Consequently, most probiotics are advertised with vague claims such as “beneficial for health”, “stabilizing gut environment”, “maintaining immune function”. These proposed benefits allow for a wide range of interpretations as they are not associated with a distinct endpoint that can be readily measured. Even without any stated health claim, due to the definition of the term probiotic (see above), its use, when administered in adequate amounts, implies benefits. More specific claims not only would allow for a better evaluation of achieving a concrete outcome, but enable individuals to choose probiotics that

provide desired benefits. Let me provide two somewhat different examples for specific health benefits to illustrate some of the regulatory issues:

1) Probiotic product X1 reduces transit time. Constipation has been targeted by probiotics [4]. While many older individuals that suffer from constipation, with transit times still in the normal physiological range, would benefit from such product, others that look for different benefits could simply ignore it. This is important as individuals desiring other benefits, such as reduced bloating, would search for products better suited for their needs. For this hypothetical product, there appears little potential for detrimental side effects. If “overdosed” individuals will know the moment they have to race to the bathroom and reduce the kind or the amount of the probiotic product they consume. If the product doesn’t yield the desired benefits for an individual it will be obvious and intake can simply be discontinued. Self experimentation with various probiotic products to find one optimally suited for an individual’s needs seems appropriate. This does not appear to be a pharmacological application, as reduction in transit time is achieved by up regulating natural processes in the gut. Nevertheless, this does not completely exclude the possibility that long term intake might have some dangers, due to microbial products that we are unaware of, or unexpected interactions with the host. After all humans have unlikely ever before been exposed long term to such large amounts of the specific probiotic strain(s) used in the product.

2) Probiotic product X2 can reduce serum cholesterol levels. Bacterial bile salt hydrolase (BSH) has been targeted for inhibiting sterol absorption and lowering serum cholesterol levels [5]. If bile acids are metabolized and excreted rather than reabsorbed in the large intestine, they have to be re-synthesized in the liver from cholesterol, lowering serum cholesterol levels. However, as the cholesterol level is highly regulated it is not clear that any short term changes after the start of probiotic intake would prevail over time. Nevertheless, it seems realistic that probiotic strains can confer drug like effects on the human host. While this appears to be a very promising utilization of a probiotic approach, there are both benefits and concerns associated with it. In contrast to example 1 medical diagnostic tests are needed not only to determine who needs to reduce serum cholesterol but also to monitor cholesterol levels resulting from probiotic intake. If such a product is effective in reducing serum cholesterol levels then there is potential to lower levels too much, which wouldn’t be obvious to the individual. This does appear a bit like a pharmacological application, as

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a new enzymatic activity is provided. Some medical supervision might be needed for such product.

Probiotics appear to neither universally fit the category of food, including medical food, nor supplement nor drug. Thus, there appears to be a need to establish an appropriate distinct regulatory framework that encourages more innovation and leads to new investment in this area. Such regulatory framework has to provide the competency required to make case by case decisions regarding expected risk/benefit ratios. Profit potential, which is the driving force behind industry investment, is likely much more limited for a probiotic food/supplement compared to a probiotic drug. Nevertheless, both industry and the public share a mutual interest, and consequently should partner in efforts to get more products that offer novel options for improving or maintaining specific health aspect efficiently to the market. While *in vitro* and animal studies can provide some relevant toxicological evidence, performing large randomized controlled trials (RCT) to establish long term safety, and whenever appropriate efficacy, appears an unrealistic requirement for every new probiotic product. Instead long term monitoring of individuals taking a new probiotic product, by utilizing the high degree of wireless internet based connectivity, might offer a viable alternative. Over time such monitoring might generate sufficient evidence to allow for better confidence and justify stronger claims regarding health benefits. Providing free probiotic product in return for participation in such monitoring efforts could stipulate participation. Individuals might be more likely to request a free product if they see a value (health benefit) in it. Thus, the proportion of individuals that request a specific free product, after they purchased it and enrolled in long-term monitoring, should correlate to some degree with perceived efficacy. Of course, separating the effects of other health behaviors correlated with probiotic intake might not be possible in observational studies.

The NIH has been proactive in this area and through its Human Microbiome Roadmap Project supported research investigating ethical issues associated with microbiota, including a project specifically exploring regulatory issues in the US associated with probiotics. It appears timely to move forward and develop a framework that provides new opportunities for the utilization of the vast potential of probiotics to improve various distinct aspects of human health. Even establishing a more generic health benefit of probiotic products would be highly meaningful IF based on quantifiable measures obtained by long term follow-up that can be readily interpreted by the general population. Longevity, disease free life years or quality of life measures come to mind. While this admittedly is an ambitious goal, it is what Metchnikoff targeted when he first proposed the concept of beneficial (probiotic) vs. putrefactive gut bacteria [6].

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