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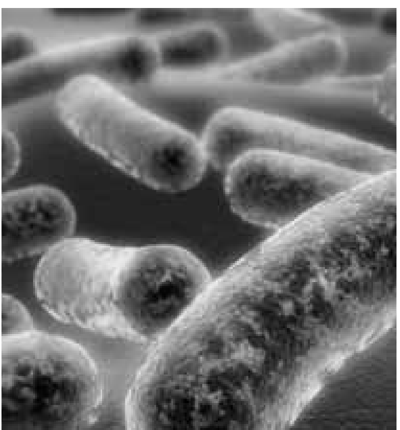
FEATURES:



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demystifying probiotics

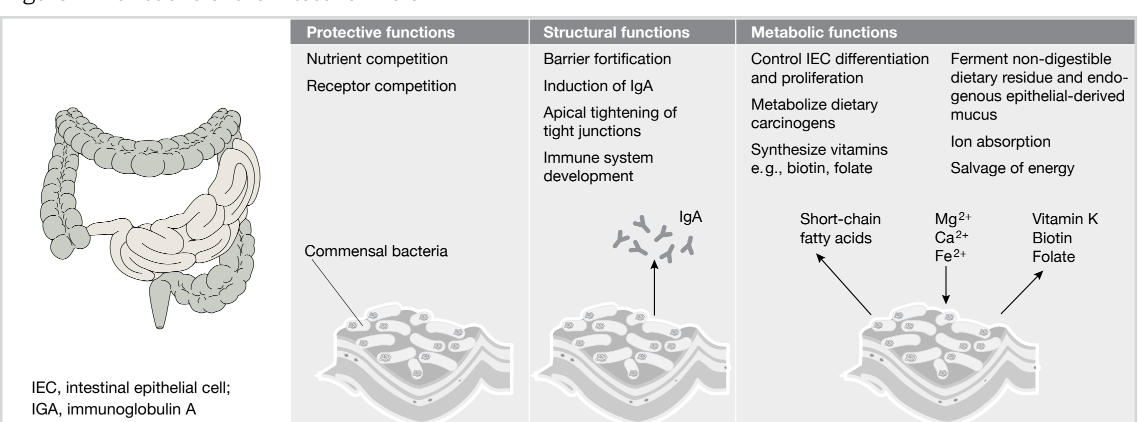
Human bodies are highly colonized, with the number of microbial cells outnumbering human cells by a factor of 10 to 1.[1] Recognizing the profound impact of microbes to human health, global initiatives are currently underway to study native microbial communities and how they correlate with human health and disease.[1] A key effort in this respect is the National Institutes of Health (NIH)-funded Human Microbiome Project, which is utilizing metagenomics to characterize human microbial communities and make this information available as a comprehensive, publicly available data set for international research efforts to understand and improve health.[1] It is likely that such research efforts will also contribute much to our understanding of probiotic bacteria, live microorganisms which have the potential of providing a diverse range of health benefits.

The insights of Mary Ellen Sanders, PhD, an industry consultant in the field of probiotics who also serves as Executive Director of the International Scientific Association for Probiotics and Prebiotics, are featured in this publication. Dr. Sanders has published extensively in the area of probiotic microbiology, collaborated on clinical studies to validate probiotic efficacy, and participated in national and international working groups convened to develop guidelines for the use of probiotics and prebiotics. She also hosts a Web site, www.usprobiotics.org along with the California Dairy Research Foundation, which provides objective, evidence-based information on probiotics for consumers and professionals.

introduction

The gastrointestinal tract contains an immense number of microorganisms which form a diverse and dynamic ecosystem, consisting of at least 10^{13} organisms, including an estimated 1000 species whose collective genomes are estimated to contain 100 times the number of genes as our own human genome.[2] The native colonizing bacteria perform various protective, structural, and metabolic functions on the intestinal mucosa (**Figure 1**), leading to the concept of the microbiota as a "virtual organ within an organ."[3] In fact, the microbiota have been called a "metabolic organ," exquisitely tuned to our physiology that performs functions that we have not had to evolve on our own.[2]

Figure 1. Functions of the Intestinal Flora[3]



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Although the myriad functions of the native microbes colonizing humans are just beginning to be understood, it is believed that certain other microbes that are consumed and added to our microbial mix—known as probiotic bacteria—may use these same mechanisms to enhance or stabilize normal colonizing microbes. Probiotics (and prebiotics) are tools for impacting the populations and activities of our normal colonizing bacteria and the physiological attributes that our colonizing microbes influence. Although not "necessarily native to our systems," Dr. Sanders explained, "probiotics may piggyback off of the same mechanisms used by our normal colonizing flora, impacting human health." With the growing appreciation for the role of the human microbiota in health and disease, a diverse range of health benefits of probiotics have been increasingly recognized.

what is a probiotic?

The term **probiotic** is a relatively new word, technically meaning "for life."[4] First introduced in 1965,[5] the definition for this term has evolved over the years, and has most recently been defined by the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) "as live microorganisms which when administered in adequate amounts confer a health benefit on the host."[4] However, there is currently no legal definition of the term probiotic in the United States. In contrast, a **prebiotic** is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health.[6] Unlike probiotics, which are live microorganisms that can act on numerous sites around the body, prebiotics are not alive, are usually carbohydrates, and act only by direct impact on the microbiota in the colon.[5]

Probiotics are typically naturally occurring microbes, such as those used in foods or isolated from humans or animals, or microbes that have been genetically altered for a specific effect.[7] Various microbes have been studied as probiotics and are available in foods and/or as dietary supplements, with the most commonly used products derived from different strains of *Lactobacillus* or *Bifidobacterium*, or the yeast *Saccharomyces cerevisiae* (boulardii).[5,8,9] Other bacteria, such as strains of *Bacillus, Enterococcus* and *Escherichia coli* are also used as probiotics.

Despite the growing interest in probiotics, there are a number of common misconceptions about these products. Probiotics are not the same as live active cultures. Live active cultures are microbes associated with foods as food fermentation agents, or starter cultures, but have not necessarily been tested for health effects.[8,9] Some live active cultures, however, have demonstrated health effects, and can be called probiotics. Thus, despite potential overlap, these terms are not synonymous. Additionally, probiotics are not synonymous with native commensal bacteria from humans, although they are commonly isolated from this source.[8,9] "Once they are shown to have health effects when administered to humans," Dr. Sanders explained, "members of our normal, commensal bacteria can be called probiotics."

> "People want to think probiotics are all one thing, but these may be very different from each other. Even different strains of the same species may have different physiologic effects. Effects seen in one probiotic cannot necessarily be extrapolated to another strain."
>
> -Dr. Sanders

Another key concept essential to understanding probiotics is that the effects of these agents are considered to be strain-, not genus- or species-specific. Despite the range of potential health benefits observed with probiotics,[10] the effects described can only be attributed to the strain or strains tested, and not to the group of probiotics as a whole.[5] Indeed, there are many examples of products marketed as different strains of the same species (e.g., *Lactobacillus acidophilus* NCFM and La-1; *L. rhamnosus* GR-1 and GG; *Bifidobacterium lactis* HN019 and BB-12), each with unique evidence documenting individual health benefits.[9] Accordingly, clinical support to substantiate clinical benefit claims must be shown for each probiotic strain. Data from studies conducted on specific strains cannot be used as evidence to support health effects of untested strains.[5] Published research shows that different probiotics can have similar effects, as is the case with several different strains that have been shown to support a healthy immune system. However, similar effects cannot be presumed for all probiotics, and studies must be conducted to support their effects.

> "Health care providers need to recognize that not all probiotics are the same. What they need to do is focus on recommending products from reliable, forthright companies that are not overstating the benefits compared to the research that's been conducted on the product."
>
> -Dr. Sanders

practical considerations for probiotic use

There are many challenges for consumers and health care professionals in choosing a probiotic. Some of these challenges stem from the marketing of these products as foods and supplements, which imposes certain regulatory limits on what benefits labels can communicate. Probiotics can be components of different categories of products, including foods, dietary supplements, medical foods, or drugs. However, most probiotics in the US are available as foods or dietary supplements, and there are currently no approved probiotic drugs in this country. Dietary supplements are products that are taken by mouth that contain ingredients (e.g., vitamins, minerals, probiotic, enzymes, etc.) that are intended to supplement the diet.[11] Dietary supplements can be available in the form of tablets, capsules, liquids, or powders.

The US government regulates dietary supplements on the basis of the Dietary Supplement Health and Education Act (DSHEA) of 1994, which was enacted to provide the legal framework specifically for dietary supplements.[11] This regulation allows for structure/function claims and claims of general well-being. Most supplements currently on the market make structure/function claims, which describe the role of the dietary ingredient intended to affect a structure or function in humans. Examples of such claims on probiotics include those suggesting that the product "supports a healthy immune system," "helps keep your microflora in balance,"[9] or helps build and maintain a healthy digestive system. Thus, structure/function claims should "promote, support, maintain a healthy body system" rather than claim that the product can treat, cure, or prevent a disease. Under DSHEA, structure/function claims must be accompanied by the disclaimer that "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."[11] Despite this required disclaimer and although structure/function claims do not require pre-approval from the FDA, the manufacturer is responsible for the accuracy and truthfulness of all claim(s).

Table 1. Criteria for a Probiotic[5,12]
• Composed of a purified strain of the microbe
• Microbe must be identified to the strain level using current techniques
• Delivered in efficacious dose through the end of the shelf life
• Shown in human studies to improve some parameter of human health
• Safe for target consumers. In the case of foods or dietary supplements in the US, the target consumer is the generally healthy population

Labeling

Misinformation regarding the content or benefits of probiotic products may also contribute to the difficulty in choosing among products. The term probiotic is sometimes used commercially even when the minimum scientific standards for probiotics have not been met.[8] Despite the lack of a legal definition for probiotic, guidelines for probiotic products have been proposed **(Table 1)**.[5,12]

Table 2. Recommended Information on Probiotic Labeling[12,13]
• Genus, species and strain
• Minimum viable numbers of each probiotic strain (CFUs) at the end of the shelf life
• Suggested serving size must deliver the effective dose of probiotics related to the health claim
• Substantiated health benefit(s)
• Proper storage conditions
• Corporate contact details for consumer information
CFUs, colony forming units

Moreover, there may be lack of third party verification that products are labeled with accurate information regarding their content. Indeed, several analyses have demonstrated that some probiotic products do not contain either the number or types of microbes specified on the label.[9,14-16] This type of inaccurate labeling may make it difficult to distinguish between substantiated and unsubstantiated claims,[9] and, as Dr. Sanders continued, "it really means that the health care provider has to do a certain amount of legwork for himself." Key information that should be included on the label of a probiotic is summarized in **Table 2**. The microbe should be identified at the genus, species, and strain level according to current nomenclature and using current best methods, providing a confidence level that the manufacturer is formulating the product with specific strains consistently over time.[9] Other important information includes the levels of live probiotic through the end of shelf life and established benefits based on human studies.

Dosage

The dose of probiotics is usually expressed as the number of colony forming units (CFUs), which is a way of expressing the number of viable microbes, per serving or dose.[13] The required dose of probiotics may vary greatly for different strains and the specific health effect under investigation, with efficacious doses ranging from 50 million to more than 1 trillion CFU/day.[9,13] Further, dose-response studies regarding probiotics are not common.[9] Thus, probiotic effects should be considered dose-specific, and it is not possible to make general recommendations about the minimum dose of probiotics that is needed for an effect.[5,8,9] Accordingly, studies documenting the efficacy of specific strains at a specific dosage cannot be used as evidence to support health effects at a lower dosage,[5] and the dose listed on the label must be based on studies that show a health effect in humans.[8]

Safety

Many species used as probiotics have been used in fermented foods and have a long history of safe use. As such, they are known to be free of infectivity or toxin production, and are thus considered to be safe for use in the generally healthy population at reasonable doses. However, since numerous different microbes can be used as "probiotics", it is important to realize that it is not possible to make general statements about the safety of the entire category of microbes used as probiotics.

Any probiotic used in a food or dietary supplement must be considered to pose "a reasonable certainty of no harm" for the target consumer. However, dietary supplements do not undergo a preapproval for safety by the FDA; assurance of safety is the responsibility of product manufacturers. A health care professional should be consulted before using probiotics for young infants or people with compromised immune systems or other major underlying illnesses. Additionally, the manufacturer of any product can be contacted regarding the extent of safety data available for specific uses. Additional factors important for assessing the safety of a probiotic include the method of administration, the level of exposure, the health status of the users, and the physiologic functions they are intended to perform.[7]

In general, few correlations between probiotic use and adverse events have been demonstrated, even though certain probiotics have been used in the food supply for decades or longer; however, few studies have specifically addressed their safety.[7] To address this situation, certain groups within the NIH and FDA have commissioned a review of available literature on safety of probiotics (specifically, strains of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*)[17] which is due to be published in 2011. Consumers should understand that although probiotics marketed as foods and dietary supplements should be safe for the generally healthy population, their safety has not been asserted on individuals with underlying health conditions.

conclusions

Human colonizing microbiota are important to health in a variety of ways. The intestinal flora, in particular, may impact health through a number of protective, structural, and metabolic functions.[3] Although these mechanisms have not been fully characterized, probiotic bacteria are believed to confer health benefits by bolstering these effects. Probiotics are a diverse group of live microbes that have been tested in humans and shown to have health benefits. However, it is essential to understand that not all probiotics are created equal, as the benefits of these agents are both strain-specific and dose-specific. Although the range of probiotic products is expanding, making clinical recommendations can be complicated by misinformation as well as the frequent disconnect between scientific evidence and allowable claims on these products. There is no legal definition of probiotics in the U.S., and all products labeled as probiotics have not necessarily been tested and shown to confer health benefits. To the contrary, some products are not validated with human studies or do not contain effective levels through the end of the shelf life. Consumers and health care professionals choosing probiotics should ensure that the health claim(s) regarding the product are substantiated with well-controlled studies and that the product has been adequately characterized for content and stability. Obtaining a probiotic from a trusted, responsible manufacturer may help ensure that the probiotic product contains scientifically validated strain(s) and is as potent through the end of the shelf life as that used in clinical trials.[13]

Although recommendations for the use of probiotics in clinical practice have not been defined, appreciation for the health benefits of these products is increasing. Recognizing that microbes profoundly shape this planet and all life on it, efforts such as the Human Microbiome Project[1] are expected to advance the science of probiotics as they further develop the concepts of how colonizing microbes and probiotics can influence human health.

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