Impact of Nutrition on the Microbiome

September 28, 2017

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NUTRITION AND THE MICROBIOME

Over the past 15 years, the scientific community has recognized the important role of the microbiome as a regulator of human health. The term “microbiome” refers to the trillions of microorganisms that naturally reside throughout the body, particularly the gut. Variations in the diversity of the gut microbiota have been linked to numerous diseases, ranging from obesity to cancer.[1-3] Emerging evidence indicates that diet exerts a powerful influence on the diversity of microbial species in the gut, carrying significant implications for health and disease. Scientific data has elucidated certain healthy eating patterns, such as diets rich in whole foods, plant fibers, and phytonutrients, each of which support a balanced gut microbiota and health maintenance throughout the lifespan.

WHY THE MICROBIOME MATTERS: GUT HEALTH AND SOCIETY

Diseases associated with changes in the gut microbiota are some of the most common and costly in developed countries. Many conditions like obesity, diabetes, cardiovascular disease, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancer, and other diseases have been linked to the typical Western diet, comprising saturated fats and processed foods.[4-6] The prevalence of obesity and diabetes, for example, has reached epidemic proportions; in the US, more than 1 in 3 adults are obese and more than 30 million have diabetes.[7-9] Diseases of the gut are also common and costly. Chron’s disease, a form of IBD, carries mean annual direct medical costs of $12,417 per patient. Overall, IBD accounts for nearly 6 million physician visits and more than 160,000 hospitalizations per year in the US.[10] Evidence links each of these conditions to the gut microbiota, suggesting that an unhealthy microbiome can have a broad and deep impact on the health of the US population.

Our growing awareness of the microbiome and its influence on common and costly disease states prompted the National Institutes of Health (NIH) to undertake the Human Microbiome Project. The aim of this program is to characterize microbial communities in the human body and to look for correlations between changes in the microbiome and human health.[11] This project is analogous to the Human Genome Project, which sought to sequence the human genome to facilitate research into genetic causes of disease. In fact, it is estimated that the microbiome as a whole accounts for more genetic information that the entire human genome, with perhaps 1000 more genes.[11] Unlike the human genome, the composition of the microbiome varies substantially between individuals and can change within an individual in response to alterations in diet, medication, disease states, and the aging process.[12,13]

FRIEND AND FOE: THE MICROBIOME

Our understanding of the microbiome and its role in health and disease has evolved tremendously in the last two decades. We now know that these microorganisms exist in symbiosis with the intestinal mucosa and are essential for gut homeostasis.[14,15] The composition of the microbiome affects the conversion of food into energy and nutrients, mucosal immunity, intestinal permeability, overall gastrointestinal (GI) health, and systemic inflammation.[1,2] Perturbations in the microbiome have been linked to the development of a variety of disorders, both directly in the GI system and through the development and perpetuation of inflammatory states common to systemic diseases, such as diabetes and arthritis.[3]

The Healthy Gut

Current evidence describes a healthy microbiome as one characterized by high microbial diversity and the ability to resist change under physiological stress.[3] In healthy individuals, the gut microbiome contributes to the digestion of foods and the generation of nutritive compounds. In fact, the microbiome is considered by many to be a metabolic organ, contributing to energy homeostasis and intestinal immunity. Bacteria in the gut

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facilitate the digestion of otherwise inaccessible nutrients, such as many starches, oligosaccharides, alcohols, and proteins, and influence ion absorption, vitamin production, and amino acid supply.[16] Finally, beneficial microorganisms compete with potential pathogens for space and nutrition within the gut and influence immune response and the differentiation and proliferation of epithelial cells.[17-20]

Here are two specific examples of how gut microbiota can influence health and disease. The first is the generation of short-chain fatty acids (SFCA) from macronutrients like carbohydrates. SFCAs, mainly butyrate, acetate, and propionate, are generated by fermentation of carbohydrates by certain gut bacteria (Figure 1). These SFCAs account for up to 15% of a person's daily energy supply and up to 70% of the energy supply for intestinal colonocytes.[16] An insufficient supply of SFCAs can impact colonocyte function and contribute to deficits in gut health. In several studies, administration of SFCAs to patients with IBD or other intestinal disorders improved GI symptoms, suggesting that components of diet may contribute to these diseases and their treatment.[16, 21-23]

A second example is the bacterium Akkermansia muciniphila, which constitutes 1%-4% of microbiota in healthy adults.[24] In human and animal studies, the abundance of A. muciniphila in the gut has been inversely associated with markers of inflammation and fasting glucose levels, as well as several disorders, including obesity, IBD, and diabetes.[25-29] Specific molecular mechanisms have been identified through which A. muciniphila may influence immune function and gut health.[30] Factors that can negatively affect the abundance of this symbiont include increasing age and consumption of a high-fat diet.[26] Conversely, administration of fruit polyphenols can increase growth of A. muciniphila, even in mice fed a high-fat diet.[31] Together, these studies demonstrate the potential impact of diet and aging on specific bacterial components of the microbiome, with consequences for health maintenance.

Dysbiosis and Disease

Reduced species diversity, fewer beneficial microbes, and the presence of harmful microbes have been associated with multiple disease states. These types of alterations to the microbiome constitute dysbiosis, which describes a pattern of microbiota associated with disease.[4] One mechanism by which dysbiosis can affect health and disease is an increase in intestinal permeability, which results in abnormal function of the epithelial barrier that lines the intestines (sometimes called the "leaky gut"). Increased intestinal permeability has been linked to autoimmune, inflammatory, and atopic diseases, among others. These changes have serious consequences for gut health and function. In IBD, for example, altered epithelial permeability increases the infiltration of inflammatory mediators through the epithelium, leading to stimulation of underlying immune cells and a reinforcing cycle of cytokine release, worsened mucosal barrier dysfunction, and increased inflammation.[32,33]

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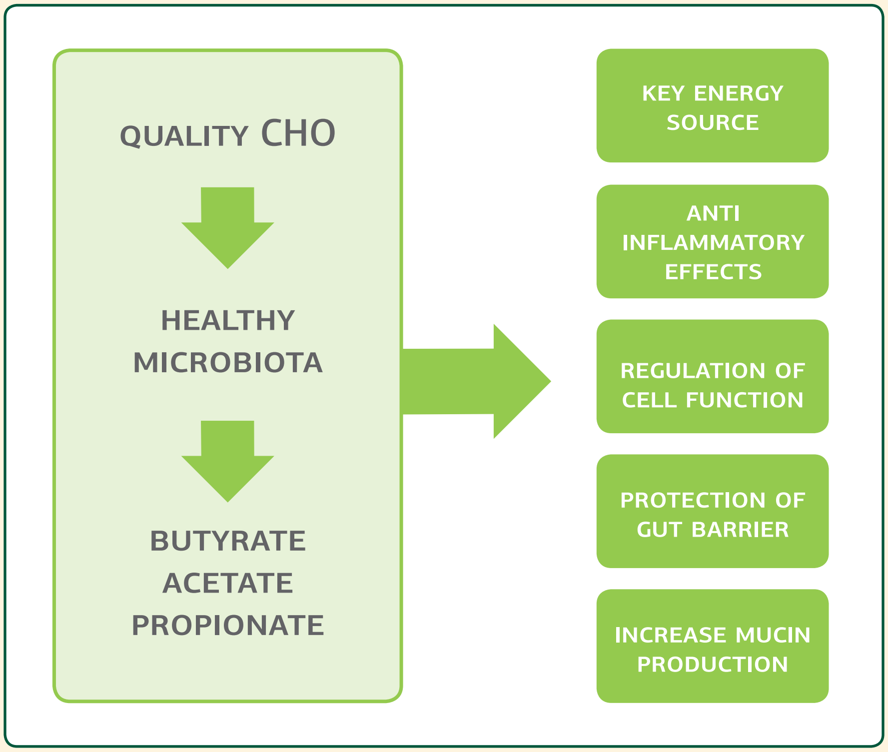
Figure 1



Quality macronutrients (eg, carbohydrates [CHO]) are converted by healthy microbiota into the short-chain fatty acids (SCFAs) butyrate, acetate, and propionate. These SFCAs support gut function and overall health through multiple actions, including protection of the gut barrier.

Factors thought to contribute to dysbiosis include diet, physical activity, host genetics, and medical therapies such as antibiotic use. The typical Western diet, one rich in saturated fats and processed foods, is strongly linked to dysbiosis and disease by a growing body of evidence.[34-40]

Although the "healthy" microbiome remains to be fully characterized, most bacterial species in normal human gut belong to the phyla Bacteroides and Firmicutes.[41] The relative proportions of these and other bacterial species vary between individuals and in many disease states. In IBD, for example, studies have described reduced proportions of Bacteroides and Firmicutes species and increased proportions of other phyla, such as Proteobacteria and Actinobacteria.[42-44] Overgrowth of Proteobacteria can lead to a reduction in bacterial species that protect the gut barrier, potentially contributing to leaky gut and increasing exposure to bacterial lipopolysaccharide (LPS), which can be toxic to the host.[45,46] Higher levels of LPS have been associated with a high-fat diet, obesity, and higher levels of proinflammatory mediators.[46]

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GUT-BRAIN AXIS

Interactions between the gut and brain (the so-called gut-brain axis) have been described in academic literature for some time. Pathways such as the autonomic and enteric nervous systems, the hypothalamic-pituitary-adrenal axis, and neuroendocrine and immune systems mediate this two-way influence. A relatively newly identified influence on this communication is the gut microbiome (Figure 2). Some gut bacteria have receptors for neurotransmitters and can even produce neurochemical substances (like serotonin and acetylcholine) that can modulate the enteric nervous system and vagus nerve, potentially affecting functions in the brain.[47-50] Certain bioactive bacterial metabolites, such as SFCA, can also stimulate the enteric and autonomic nervous systems.

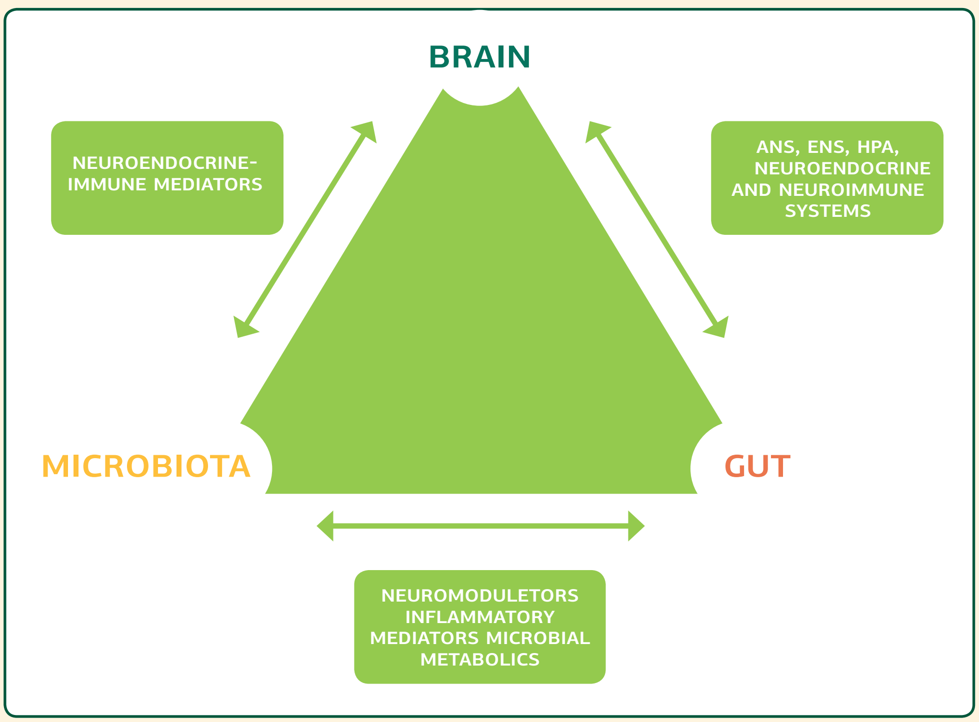
The pathway is bidirectional. Signals from the central nervous system related to stress or emotion can modulate the production of mucus (an energy source for some gut bacteria) and antimicrobial peptides in the gut, as well as intestinal permeability and motility.[47-50] Bacterial gene expression may be affected by neurochemicals, such as norepinephrine. Together, these mechanisms and others may alter the composition and diversity of the gut microbiota.

The health of the microbiome, therefore, may not only influence common systemic diseases, but brain function and health as well. Stress or other psychological factors may in turn affect the health of the microbiome.

AGE AND THE MICROBIOME

The composition of the microbiome changes with age. The initial colonization of the gut and other sites begins at the time of birth, when neonates are exposed to the mother's urogenital microbiota.[52] Influences of early microbiome development include the method of delivery (C-section vs. vaginal), hygiene, breast milk, and environmental factors.

Figure 2. The Gut-Brain-Microbiome axis



Evidence suggests that bacterial products can modulate nervous system function, which in turn can affect gut function and microbiota through neuromodulatory compounds and changes in mucus production and intestinal permeability. ANS: autonomic nervous system; ENS: enteric nervous system; HPA: hypothalamic-pituitary-adrenal axis. Adapted from Sirisinha et al.[51]

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With aging, the microbiome evolves considerably. The microbiome reaches its full diversity sometime during adolescence. However, the greatest alterations in the microbiome have been documented in older adults.[52] Studies in older adults have correlated diet and gut microbiota with inflammation and a variety of common age-related conditions, including frailty, Clostridium difficile colitis, and atherosclerotic and metabolic diseases.[53]

DIET AND THE MICROBIOME

The increasing prevalence of obesity, diabetes, cardiovascular disease, and other conditions corresponds to changes in the Western diet that include higher proportions of fat and refined carbohydrates and lower amounts of fiber and other plant-based nutrients. Until recently, research focused on the direct links between specific nutrients and excess calories on disease states. Current research defines a role for the microbiome in mediating the interaction between genetics, diet, and health.

The impact of a typical Western diet on the microbiome is illustrated by studies that demonstrated greatly reduced diversity of gut microbiota in people from the US compared to rural native populations in South America and Africa.[54,55] Similar disparities were found between hunter-gatherer and agrarian-based people within the same region, suggesting that a Western-style diet may be responsible for the loss of microbial diversity in the gut.[55] Differences in diet (and possibly in the microbiome) likely contribute to the very low incidence of Western diseases like diabetes and obesity among native populations, as compared to epidemic proportions in developed countries.[16]

Table 1. The effects of specific diets on the microbiome[13,19,56-60]

Diet	Microbiota affected	Effects
High fat	**Reduced:** *Bacteroides* *Firmicutes*	Decreased microbial diversity, increased bowel permeability, increased bile acid secretion
Reduced carbohydrate	**Reduced:** *Bifidobacteria, Clostridium* *Bacteroides, Akkermansia*	Decreased SFCA production and fiber-derived phenolic acids
High protein	**Increased:** *Bacteroides, Lactobacillus* *Bifidobacteria*	Beneficial compounds from proteolytic fermentation but toxic products from putrefaction
FODMAP	**Reduced:** *Bifidobacteria* **Increased:** *Actinobacteria*	Improves IBS symptoms in some patients

13. Lopez-Legarrea P, Fuller NR, Zulet MA, Martinez JA, Caterson ID. The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state. Asia Pac J Clin Nutr. 2014;23(3):360-368.
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Macronutrient Diets and the Microbiome

Depending on the proportion of macronutrients (fat, protein, carbohydrate) in a diet, the microbiome may differ as well (Table 1). High-fat diets, for example, are associated with reduced proportions of Bacteroides and increased Firmicutes, with overall reduced microbial diversity.[56] High-fat diets also may foster increased bowel permeability through changes in the gut microbiota. Dietary fat may indirectly modulate gut microbiota through changes in bile acid secretion; bile acids have selective antimicrobial activity and may mediate some of the changes in microbiota associated with a high-fat diet.[57]

Although there are few studies on the effects of high protein levels on the gut microbiota, some changes in the microbiota have been noted in association with a high protein diet. High protein diets, such as those commonly used for weight loss, have been associated with lower abundance of Bifidobacteria, Akkermansia, and other beneficial bacteria, as well as reduced production of the important SFCA butyrate.[58-60] Dietary protein content may influence the means by which proteins are broken down in the gut. For example, when consumed in moderate amounts, the digestion of proteins through proteolytic fermentation can generate polyphenols with anti-inflammatory and antioxidant effects. Conversely, putrefaction of proteins by anaerobic bacteria can produce potentially toxic substances, such as ammonia, amines, phenols, thiols, and indols.[19]

The findings of studies of diets with differing macronutrient contents must be considered with caution. A change in the proportion of one macronutrient has a corresponding effect on other macronutrients – in other words, a high-fat or high-protein diet is likely to be low in carbohydrates. Therefore, the specific effects of a high-protein diet on the microbiome, for example, may be difficult to discern from the accompanying impact of reduced carbohydrate content.

Therapeutic Diets: FODMAP

Some specific diets have gained popularity for the management of GI disorders, such as IBS. One example is the low FODMAP diet, which restricts intake of certain short-chain fermentable carbohydrates (oligosaccharides, disaccharides, monosaccharides, and polyols). Some studies have shown this diet to improve IBS symptoms and it may also affect the microbiome. In patients with IBS, studies have reported reduced abundance Bifidobacteria and increased Actinobacteria associated with low FODMAP diets.[61-63] Although it is hypothesized that the efficacy of this diet may relate to reduced microbial fermentation in the gut, the clinical significance of documented changes to the microbiome remain unclear.

USING NUTRITION TO FOSTER A HEALTHY MICROBIOME

The consumption of certain specific nutrients can help to minimize inflammation, normalize intestinal microbiota, and restore epithelial integrity. Diets rich in vegetable fibers and phytonutrients, for example, can foster bacterial species that ferment dietary fiber, leading to higher concentrations of SFCAs, which can protect against bowel inflammation.[64-66] Indeed, research has identified multiple dietary components that can improve the diversity and health of the microbiome. These components include prebiotics (such as plant fibers), probiotics, and phytonutrients, which are typically underrepresented in Western diets.

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Probiotics

Probiotics consist of live bacterial and/or yeast cultures that are consumed in foods. These microbes compete with pathogenic microbes for resources and may alter the composition of the microbiome. They can also modulate immune response, reverse intestinal permeability, reduce cholesterol levels, and improve lactose digestion in lactose-intolerant people, among other benefits.[67-69] To be effective, probiotic bacteria must be resistant to acid and bile in the upper GI tract. However, even resilient bacterial strains do not durably alter the gut microbiota and therefore must be taken regularly to maintain clinical benefits.

The fermented dairy products yogurt and kefir are examples of probiotic-containing foods. In animal models, consumption of kefir leads to an increase in the beneficial bacteria Lactobacillus and Bifidobacteria and decreases in Clostridium species.[70] Changes in the growth rate and gene expression of Bifidobacteria have also been documented, which may facilitate immunomodulation and adherence to the gut.[71]

Probiotics are commonly used to treat post-antibiotic diarrhea and may have utility for some patients with IBS or other GI conditions.[69] Probiotics may also play a role in the management of small-intestinal bacterial overgrowth (SIBO), which is a common form of dysbiosis.[72] This condition can result from the failure of mechanisms that regulate microbiota in the small intestine and is associated with flatulence, bloating, diarrhea, and abdominal pain. Overlap with IBS is common. Antibiotics are typically used to treat SIBO, but some evidence suggests that probiotics can improve symptoms and may enhance the effectiveness of antibiotics.[72,73]

Prebiotics

Prebiotics are commonly defined as food ingredients that are not digestible by the human gut but confer health benefits to the host through modulation of specific gut microbes.[74] In general, these compounds encourage the growth of Bifidobacteria and Lactobacilli, both of which are anaerobic bacteria that break down carbohydrates in the gut.[75] Foods that stimulate bacterial fermentation lead to an increase in bacterial mass in the colon and therefore an in increase stool bulk.[76] Examples of prebiotics include non-digestible oligosaccharides and dietary fibers composed of fermentable carbohydrates.[77] Common foods that contain oligosaccharides include leeks, onions, garlic, wheat, and oats. Consumption of oat-based foods has been linked to reduced cholesterol levels and reduced gut inflammation, among other actions.[78,79] Both oat bran and buckwheat foster the growth of beneficial gut bacteria, such as Lactobacillus.[80]

Evidence suggests several major benefits with prebiotics, including increased production of SFCAs, improved gut barrier function and immunity, reduced inflammation, and reduced pathogenic bacteria.[76] Clinical studies have reported changes in gut microbiota, reductions in cholesterol and peak postprandial glucose levels, and immunological improvements associated with the consumption of whole-grain (ie, prebiotic-containing) foods.[81,82] Although the amount of prebiotics in many foods may be too low to significantly affect gut microbiota, the extraction of prebiotics from plant sources allows for fortification of foods to provide sufficient amounts to modulate the gut microbiome.[83,84]

Phytonutrients

Plants develop bioactive compounds called phytonutrients (or phytochemicals) to protect themselves from various threats, such as fungi and insects. These phytonutrients are plentiful in fruits, vegetables, legumes, and grains and have multiple health benefits for humans.[85] Many thousands of phytonutrients have been described; the broad classes relevant to human nutrition include carotenoids, phytosterols, and phenolics.

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Current evidence suggests that gut bacteria are integral to the metabolism and absorption of phytonutrients and their metabolites.[86] Furthermore, phytonutrients can modulate the microbiome. For example, the consumption of certain berries that are rich in polyphenols, such as cranberries, blueberries, and grapes, can increase the abundance of Bifidobactertia and Akkermansia. Studies in mice found that administration of a polyphenol-rich cranberry extract over 8 weeks led to a large increase in the abundance of beneficial Akkermansia.[87] Consumption of polyphenols such as quercetin and those found in pomegranate can also increase the abundance of Akkermansia.[88,89] Separate studies have linked consumption of blueberries and red wine to increases in Bifidobacteria.[90,91] Quercetin, one of the most common polyphenols in fruits and vegetables, has been shown to alter gene expression in important gut bacteria, such as Bifidobactera, Enterococcus, and Ruminococcus.[92]

Recent research links certain phytonutrients, those associated with bitter taste, to alterations in glucose absorption and utilization. Receptors that sense bitter taste are present throughout the gut, and activation of certain bitter receptors in the gut have been shown to delay glucose absorption and increase the utilization of glucose.[93] This evidence suggests yet another mechanism by which phytonutrients may influence metabolic control and overall health.

Soil Microbiome and Plant Nutrients

One final important point regarding the benefits of plant nutrients has to do with how plants are grown and the impact of the soil microbiome. Differing farming techniques – for example, organic versus conventional farming – have been shown to alter the microbiome of the soil itself. Studies of organic farming systems demonstrate a more heterogeneous soil microbiome and greater nutrient availability to plants, in addition to other benefits.[94,95] And organic farming has also been linked to improve phytonutrient composition in plants – which as discussed can improve the health of the gut microbiome.[96] For example, a meta-analysis of 343 studies found that a range of phytonutrients, including quercetin and other flavonoids, were present in higher concentrations in crops grown organically, compared to conventionally-grown crops.[96] Investigation into the influence of the soil microbiome on plant and human health is just beginning. Current findings suggest that organic farming practices can alter the soil microbiome, which affects plant health and phytonutrient content, with implications for the human microbiome and health.

CLINICAL ROLE OF THE MICROBIOME

Taken together, current evidence suggests some approaches to the management of common conditions through modulation of the microbiome. Evidence clearly supports the benefits of diets that are rich in whole foods – whole grains, vegetables, and fruit – for overall health. These foods contain multiple important nutrients, including prebiotics and phytonutrients, that support the growth and maintenance of a healthy and diverse microbiome. A healthy microbiome in turn supports the production and absorption of nutrients such as SFCAs, vitamins, and antioxidant and anti-inflammatory compounds that can reduce systemic inflammation, improve glucose homeostasis, and limit intestinal permeability.

Other clear avenues for therapy include the use of probiotics to improve post-antibiotic diarrhea.[69] Evidence supporting the use of probiotics for other conditions is more limited. However, probiotics are a useful adjunct to diet that can support immune function and ameliorate symptoms of IBS in some patients.[69,97] Some data suggest benefits to the use of probiotics such as Lactobacillus preparations in fostering weight loss[98] and improving anxiety, stress, and depression,[99] although most studies have had small sample sizes or other methodological limitations. Doses found to be most effective in clinical studies are often >5 billion CFU (colon-forming units) in children and >10 billion CFU in adults. However, the type of probiotic is more important than the quantity. Examples of beneficial probiotic strains include Lactobacillus sp., Bifidobacteria, and Saccharomyces (Table 2).

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Table 2. Specific probiotic strains and their demonstrated health benefits.

Probiotic strain	Health benefits
Lactobacillus rhamnosus GR-1	Prevents growth of harmful microbes[100,101]
Lactobacillus acidophilus	Prevents growth of harmful microbes Improves constipation, lactose intolerance, symptoms of IBS[102-104]
Lactobacillus paracasei ssp paracasei	Improves immune function, adheres to host gut and inhibits harmful microbes[105,106]
Lactobacillus salivarius ssp. salivarius	Anti-inflammatory effects, inhibits harmful microbes[107,108]
Bifidobacterium lactis	Improves immune function, improves constipation and GI symptoms[102,106,109]
Saccharomyces cerevisiae var. boulardii	Fosters normal gut function, anti-inflammatory effects[110,111]

Synbiotics

The combination of both probiotics and prebiotics is called a synbiotic. The prebiotic improves the survival of the probiotic bacteria and stimulates the activity of host bacteria. In studies, administration of synbiotics to patients following surgery for liver conditions or multiple-trauma led to a reduction in the incidence of infectious complications.[112,113] In patients with non-alcoholic fatty liver disease, symbiotic treatment led to a reduction in liver fat.[114]

Although preliminary, these data suggest a role for probiotics, prebiotics, and both together (synbiotics) in the maintenance of overall health, the prevention of infection, and the treatment of certain disease states.

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