CHAPTER 1.4

The Gut Microbiome

Sarah Ashman*, Hari Krishnamurthy†

*Clinical Education, Vibrant America Clinical Laboratory, San Carlos, CA, United States,
†Technology Development, Vibrant Sciences, San Carlos, CA, United States

INTRODUCTION

The human superorganism is a collective term for our human bodies and the microbes they host, mostly symbiotic but occasionally pathogenic. The superorganism can be thought of as an interdependent ecosystem in which microbes rely on the host for necessary sustenance in order to thrive and in turn provide the human host with critical support functions such as immunomodulation.

Technological and computational advances in genome studies have enabled the study of the human microbiome, which is an order of magnitude higher in complexity compared with the human genome by itself. Much of the work in this field has been accomplished since the Human Microbiome Project started in 2007 by the National Institutes of Health. The first phase of the project involved the basic characterizing of human microbial flora. The second phase, called the Integrative Human Microbiome Project (iHMP), was started in 2014 with the aim of studying the role of microbes in health and disease states and is expected to lead to new discoveries in diagnosis, prognosis, and treatment of a variety of human diseases [1].

TECHNOLOGICAL APPROACHES TO STUDYING THE GUT MICROBIOME

DNA Approaches—What Is Present?

The complexity of the gut microbiome with its variety of species is challenging to study. A culture-independent method of evaluation is critical, because many of these organisms have never been cultured and it is unknown if novel growth conditions are necessary to culture some [2].

Effects of Lifestyle on Men's Health. https://doi.org/10.1016/B978-0-12-816665-9.00004-4

Initial studies in this space with bacteria involved targeted sequencing of specific regions such as 5S and 16S rRNA genes [3]. Though this method contributed to significant understanding of the microbiome, large-scale studies were not possible until the advent of next-generation sequencing. Sequenced organisms were grouped into operational taxonomic units and referred to as a single bacterial species when the sequence similarity was 97% [4]. Although more progress has been made in the study of bacteria than viruses and eukaryotic microbes, considerable efforts are now being made to reduce this imbalance. Viruses are primarily studied using shotgun sequencing and microarrays [5], while eukaryotic organisms are studied using 18S rRNA and specific signature sequences [6, 7].

RNA Approaches—What Is the Functional Pathway?

Apart from DNA-based studies, studies have also been done based on the RNA of these organisms that are referred to as metatranscriptomics. It is estimated that the microbiome expresses 100 times more genes than the human host. The activity of the microbiome can be gauged by studying microbial mRNA via sequencing. The main challenge in this space has been the stability of the RNA, which is being addressed in novel methods to extract and study it [8].

DIFFERENTIATION OF THE INTESTINAL MICROBIOME

Protein and Metabolite Approaches—Host Interaction and Outcome

Metaproteomics is the study of the microbial proteome, which is expected to give us a better understanding of how the gut microbiome interacts with the host. The complexity of looking for multiple proteins enables researchers to look at the functional characteristics and activity of the gut microbiome [9]. Another aspect of the gut microbiome is the study of the metabolites produced by them. These small molecules have been shown to affect the physiology and even modify the intestinal permeability of the host [10]. Both metaproteomics and metabolite studies of the gut microbiome are relatively new but hold promise to a better understanding of the human superorganism.

Within the superorganism, multiple microbiomes exist. An integumentary microbiome interacts with the external environment; a salivary microbiome can be either protective or destructive to oral health [11]; the intestinal microbiome is probably one of the most well known and studied of late; and the genital microbiome(s) [12], according to some animal studies and depending on gender, might influence reproductive health and possibly even epigenetics of offspring [13].

The intestinal microbiome has gained notoriety recently due to its pivotal role in human health. While current research into the intestinal microbiome is merely scratching the surface of what humans can know about their microscopic symbionts, much has already been elucidated in regard to this complex relationship. The majority of research has occurred and still does occur in animals; however, within the last decade, a significant number of human trials, both in vivo and in vitro, have begun to fortify the knowledge base and further explore the interplay of humans and microbes as they relate to a variety of disease states, nutritional outcomes, and epigenetic influences.

Broad Functions

The intestinal microbiome plays a number of roles in human health, from very complex immunomodulatory functions to broad influence on nutritional status. Microorganisms included in the intestinal microbiome include bacteria, yeasts/fungi, and sometimes parasites. Bacteria can be classified into three main groups: **commensal** microorganisms (those acquired through exposure over the life span and that help the host symbiotically), **pathobionts** (bacteria normally found in the intestinal tract, perform some beneficial functions, and whose populations may also be opportunistic without adequate commensal abundance), and **pathogens** (bacteria that cause disease and should not be found in any normal intestinal microbial ecosystem).

The main functions of the intestinal microbiome consist of immunomodulation, fiber fermentation, vitamin production, inflammatory response, competitive inhibition of pathogens, and mucosal barrier fortification. Refer to Table 1 for greater detail on each of these functions.

MICROBES AND IMMUNITY

T-cell differentiation is one of the primary immunomodulatory influences that microbes have on the host's immune system. T-cell differentiation is the act of T helper cells (Th) becoming regulatory T cells, or Tregs, and preventing unchecked Th17 immune responses. This occurs partly through the production of the short-chain fatty acids (SCFAs), butyrate, propionate, and acetate, which are the by-products of fiber fermentation by microbes in the colon. SCFAs bind to G-protein-coupled receptors (GPCRs) on intestinal epithelial cells and influence the activation or differentiation of T cells, in a dose-dependent manner [33]. SCFAs have differing mechanisms of influence on T-cell differentiation depending on which SCFA is acting. Refer to Fig. 1 for an illustration of specific mechanisms of SCFAs on T cells.

Table 1 Broad Functions of the Intestinal Microbiome

Major Function	Central Concepts
Immunomodulation	1. Recognition of immune-stimulatory bacterial molecules and microbial metabolites shapes the innate immune system [14] 2. The absence of sufficient microbial populations and their microbial metabolites has downstream effects on immune function in the host [15]
Fiber fermentation	1. The human host's survival depends on its microscopic intestinal symbionts, as they depend on the host for both real estate and sustenance 2. The majority of microbiota are capable of fermenting fiber, simple carbohydrates, and even complex carbohydrates 3. Microbial abundance relies on the abundance of metabolites produced by other microbes [16], and the amount and types of fiber being fermented are just as relevant as the consistency or frequency of intake [17]
Vitamin and nutrient metabolism	1. The primary vitamins that intestinal microbes are known to liberate or synthesize are the B vitamins (primarily B12, B6, and folate) and vitamin K2 [18, 19] 2. Humans lack B vitamin absorption mechanisms in the large bowel where the majority of vitamins are synthesized [20, 21]. Animal studies, however, have shown that some B vitamins may be absorbed into circulation [18] 3. Oxalate-degrading microbes in the intestinal tract affect the absorption of oxalate as evidenced by urinary excretion rates and reduced incidence of renal calculi [22–24]
Inflammatory response	1. Intestinal microbiota modulate inflammatory responses, both locally in the intestines and systemically outside the gastrointestinal tract [15, 25, 26] 2. If certain groups of commensal microorganisms are not acquired or cannot thrive, the host lacks some degree of immune development [27–29]
Competitive inhibition of pathogens	1. Commensals crowd out opportunistic and pathogenic microorganisms, preventing them from adhering to luminal surfaces [30] 2. Commensal bacteria also perform interference inhibition by producing antimicrobial peptides (AMPs) that limit or suppress the growth of pathobionts and pathogens [30]
Mucosal barrier fortification	1. Commensal microbes in the mucosa provide metabolites that fortify the epithelial barrier through paracellular tight junction modulation, cellular cytoskeleton fortification, and short-chain fatty acid (SCFA) production [31, 32]

Homeostasis Is Maintained by Two-Way Communication Between the Microbiota and Intestinal Immune System

All biological systems and organisms will seek to maintain or return to homeostasis as a primary goal of survival. Maintenance of homeostasis relies upon delicate systems of communication between the host and the intestinal microbiome. The mutual survival of both parties is the ultimate goal. The primary methods of communication occur through metabolites produced by the microbes [34], antimicrobial peptides produced by the host and the microbes [30], and lipopolysaccharide (LPS) or lipoteichoic acid (LTA) on the outer membrane of microbes that allow the host immune system and other microbes to easily recognize friend from foe [35].

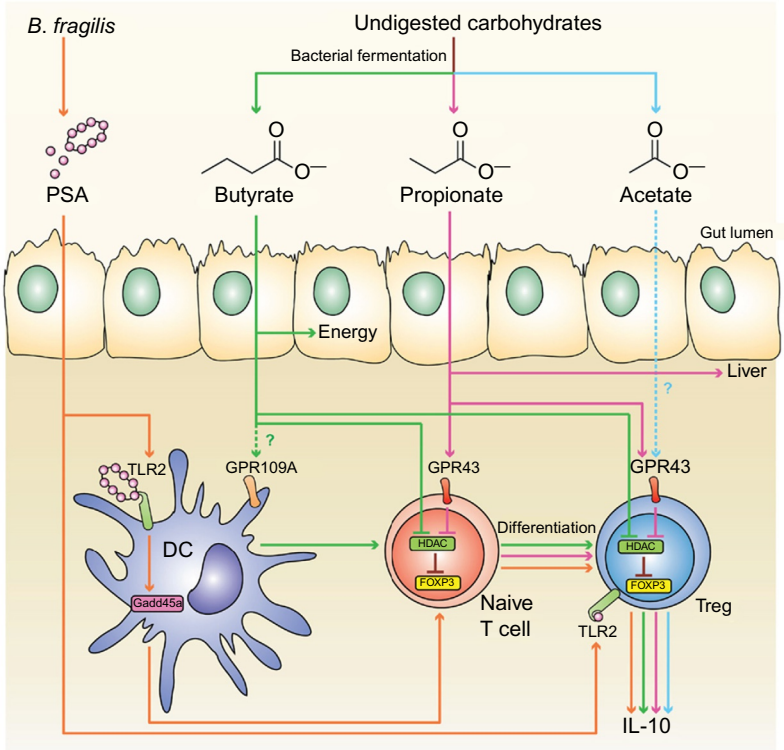

FIG. 1

Direct and indirect influence of short-chain fatty acids on immunomodulation through T-cell differentiation. *From: Hoeppli RE, Wu D, Cook L, Levings MK. The environment of regulatory T cell biology: cytokines, metabolites, and the microbiome. Front Immunol 2015;6:61. https://doi.org/10.3389/fimmu.2015.00061.*

Metabolites are able to modulate host immune responses [15], influence metabolism of nutrients [36], and even affect neurological processes such as appetite and mood [37]. These metabolites produced by microbes include SCFAs, such as butyrate, propionate, and acetate; lactic acid; and vitamins, such as K2 and biotin [38]. SCFAs from fermentable carbohydrates specifically modulate immune responses such as T-cell differentiation [33], promote satiety [39], and even modulate host gene expression through histone deacetylase activity [40].

The aforementioned antimicrobial peptides (AMPs) produced by intestinal microbes are capable of inhibiting the growth of pathobiont and pathogenic microorganisms and are released by commensal organisms when invasive microbes are sensed in their specific niche of the intestinal ecosystem. AMPs such as defensins and cathelicidins are also produced by the host to shape the intestinal microbiome of commensals and pathogens and are produced by cells in the Peyer's patches in response to changes in concentration and location of both commensal and invasive microorganisms [41]. The main

mechanism of action of AMPs against various bacterial species is their ability to bind to bacterial membranes and disrupt them, leading to cell death [42]. Without adequate abundance of commensal microorganisms in the intestinal mucosa, production of AMPs for competitive inhibition of opportunists and pathogens is reduced.

One last category of metabolites that are produced by microorganisms and participate in modulation of the microbiome and host immune response is bacterial endotoxins: LPS produced by gram-negative bacteria and LTA produced by gram-positive bacteria.

LPS is a potent bacterial endotoxin involved in inflammatory stimulation of the host immune response by binding to toll-like receptors (TLRs) [35] in the local luminal sites, where it causes an increase in intestinal tight junction permeability, which allows relatively unchecked paracellular flow of substances from the luminal side to systemic circulation [43]. If LPS translocates across an impaired intestinal barrier [44], it has been linked to the development of the inflammatory precursors to metabolic syndrome, obesity, and type 2 diabetes [45]; propagation of inflammatory conditions such as osteoarthritis [46] and even neurological symptoms in vivo in mice and in vitro human studies [47, 48]; and, in severe cases of impaired immune function, septic shock [35].

LTA has a very similar mechanism of action in binding to TLRs, which initiate inflammatory responses from the host. Once it has bound to its ligand, the same types of inflammatory cytokine responses result from the host [35, 49].

MICROBIAL DIVERSITY

The key to a healthy intestinal microbiome in humans is diversity [50]. Taxa of microbiota rely on each other for sustenance and defense of their niches. With the loss of abundance of one group, others also decline. Thus, the symbiotic nature of the microbiome is not only as it relates to the host and microbes but also as microbes relate to one another.

The concept of diversity of the intestinal microbiome can be summarized as follows: the greater the number of species, the greater the entire system is at adapting and surviving. Low diversity is correlated with a number of chronic diseases including irritable bowel syndrome (IBS) [51], inflammatory bowel disease (IBD) [50], colorectal cancer [52], celiac disease [53], obesity [54], and even autism [55]. While human studies are merely beginning to elucidate cause-and-effect relationships between alterations in the intestinal microbiome and host disease, some have already shown that these microbial alterations, or dysbiosis, are at least not the result of the disease, but more likely to have been present before disease onset and, therefore, involved in its progression or

exacerbation [56–58]. While long-term human studies are still pending, animal studies have shown so far that over four generations of nutritional changes that affect microbiome diversity, the low diversity of the intestinal microbiome becomes permanent in the host [59].

Keystone Species

Exposure to a variety of microbes throughout the earliest years of life is one of the critical components of the microbiota's development and maintenance. The concept of keystone species refers to those species that, in humans, are considered important, if not critical, to balanced immune responses, interconnected interactions with other taxa, proper homeostasis of the intestinal tract, and the host's long-term health. Taxa that have been identified as keystone groups include *Lactobacillus*, *Bifidobacterium*, *Eubacterium*, *Clostridia*, *Butyrivibrio*, *Roseburia*, *Akkermansia*, *Faecalibacterium*, *Bacillus*, *Prevotella*, *Lachnospiraceae*, *Ruminococcus*, *Oxalobacter*, and *Blautia* [60].

Diversity is acquired early in life from birth to as late as 5 years of age but does continue to evolve over the life span of the host in response to environmental influences [61]. Infants born via vaginal delivery acquire a microbiome that differs from those born via cesarean delivery [62]. Vaginally delivered infants acquire the first inhabitants of their internal microbiome within hours of birth, via vaginal and fecal exposure from their mother [63]. Infants fed primarily breastmilk tend to have much richer *Bifidobacterium* and some *Lactobacillus* abundance from these microbes naturally present in breastmilk [64]. As infants begin to add solid foods more indicative of adult eating patterns, such as complex carbohydrates, their microbiome fluctuates to resemble that of an adult pattern more closely [63].

While birth and early diet initially impart diversity, environment influences the development of diversity in the microbiome. The host's continued exposure to its surroundings is also a major contributory factor in the development of microbial diversity. The hygiene hypothesis suggests that children (and adults) who experience a greater diversity of microbes earlier in life have stronger immune systems, which can adapt to a greater number of threats without long-term harm to the host, and less incidence of chronic inflammatory diseases later in life [27–29, 65, 66]. Both early-life exposures to diverse environments through birth and breastfeeding provide important exposure to microbes, while environmental influences contribute as humans age.

Metabolic Crossfeeding

Another central concept to the microbiome's balance and adaptability is metabolic cross-feeding between taxa. Bifidobacteria can cross-feed with certain

butyrate producers [16], for instance. This means that one bacterium produces a by-product or metabolite that feeds another. The *Lactobacillus* genus is well known for its production of lactic acid, which is used by other species, such as *Anaerostipes caccae*, to produce butyrate [67]. When levels of the primary genus fall, the secondary genera that rely on its metabolites are affected as well [67, 68]. In order to bring balance and homeostasis, consideration must be given to the interrelated nature of the ecosystem and not just one or two keystone species.

Suppressing Diversity Through Prescription Antibiotic Use

Use of prescription antibiotics is a critical and lifesaving tool for health-care providers. Because of widespread overuse in past decades, however, many species of microorganisms have grown tolerant or resistant to many antibiotics [69, 70]. Additionally, because recommending a probiotic supplement alongside an antibiotic drug is still not common in many health-care providers' protocols [71], research is discovering that individuals with multiple courses of antibiotics are often lacking sufficient abundance of keystone microorganisms, which have been almost permanently suppressed through that antibiotic use [72].

The use of probiotics concurrently or immediately following a course of antibiotics has been shown to lessen the side effects of antibiotics and may prevent some loss of microorganism diversity typically seen with standard and routine antibiotic use [71, 73–75].

Antibiotic effects on diversity are variable. A study conducted with 21 patients treated with broad-spectrum antibiotics found that patients saw an average of 25% reduction in microbial diversity found in fecal samples after antibiotic administration, and the number of taxa present fell from 29 to 12; furthermore, analysis revealed that taxa in the gram-negative groups grew in abundance in relation to the gram-positive microbes, causing a shift in gram-positive to gram-negative balance, which may explain inflammatory symptoms such as diarrhea [76]. Abundance of commensal microorganisms, particularly some SCFA producers, may be affected between 40 days [77] and 4 years [72] post treatment, while the *Firmicutes-Bacteroidetes* ratio increases in favor of Firmicutes, which has been linked to inflammatory conditions such as obesity [78, 79] and a lower competitive inhibition of pathogens [80].

COLON HEALTH AND COLORECTAL CANCER

Perhaps, one of the most beneficial discoveries of microbiome research in human health is the connection between SCFA levels in the colon and T-cell differentiation, immunomodulation, colitis, and colorectal cancer. The effect

of butyrate levels on T-cell differentiation has been extensively researched in the pursuit of better understanding of chronic inflammatory diseases.

Butyrate's main contribution to immunomodulation in the intestinal lumen and colonocyte is its influence on T-cell differentiation through GPCRs, which influences those T cells' response to antigens, from sources such as diet, microbes, and environmental chemicals [33]. In two in vitro studies, one pathway through which butyrate's immunomodulation was shown was the inhibition of NF-κB [81] and modulating gene expression to reduce the risk of colorectal cancer [40]. It is this latter effect that is of particular importance to many health-care providers, as the early detection of colorectal cancer has contributed to a significant reduction (20%) of new colorectal cancer cases [82]. The risk for developing colorectal cancer is also slightly higher in men (4.49% over one's lifetime) than in women (4.15% over one's lifetime) [83].

Butyrate is not the only SCFA produced by colonic bacteria that benefits the colonocytes and intestinal immunity. Acetate and propionate are also by-products of fiber fermentation in the colon and have broad influence on T-cell differentiation through different mechanisms but yield the same overall result: greater immunomodulation to reduce aberrant immune responses, in addition to increases in *Lactobacillus* genus, *Lachnospiraceae* family, and an abundance of *Akkermansia* [84].

Abundance of SCFAs is correlated with lower risk of colitis [85]. SCFAs bind to GPCRs to stimulate production of Tregs, the abundance of which controls or influences inflammatory responses [86]. Increased inflammatory responses are associated with increased incidence of colitis [87], which, if left untreated, has a higher incidence of tumorigenesis and colorectal cancer [85].

MEN'S HEALTH AND THE GUT MICROBIOME

The gender of the host has been shown to affect the gut microbiota composition [88]. Specifically, some studies have also shown that gender-specific immune system modulation could be attributed to the gut microbiota [89, 90].

Gut Microbiome and Testosterone

Male obesity has been associated with decreased testosterone production and lowered fertility. A high-fat- or high-calorie-based diet affects the gut microbiome and could result in intestinal permeability leading to the circulation of LPS, which in turn could result in the body lowering testosterone production to help fight infections [91]. Testosterone is a known immunosuppressant, and it has been postulated that lowering testosterone could have resulted in evolutionary benefits to fight infection [92, 93].

Gut Microbiome and Prostate Health

Several studies have been conducted on the role of the gut microbiome in the pathogenesis of prostate cancer. One such study observed higher abundance of *Bacteroides massiliensis* in prostate cancer cases as compared with controls [94]. Meta studies have indicated multiple anatomic sites involved in prostate health and disease [95]. Dysbiosis of the microbiome could lead to inflammatory response that increases the chances of diseases at different anatomical sites. A novel microbiome-derived risk factor for prostate cancer based on 10 aberrant metabolic pathways has also been proposed [96]. Overall studies in this space are still preliminary, and more extensive studies are needed to understand the underlying relationships.

Cardiovascular Health

Due to technological limitations, the connection between the gut microbiome and cardiovascular inflammation has not been fully elucidated. The model of microbial influence on atherosclerosis has been studied in great depth in animals; however, human trials are still ongoing. Previous findings show that there is a direct and indirect influence from the periodontal microbiome on immune dysregulation and inflammation that precipitate atherosclerosis through disruption of endothelial cell function [97].

Making a leap to the contribution of inflammation from intestinal microbiota to atherosclerosis is much more complex. There appear to be mechanisms with potential influence on the development and propagation of inflammatory arterial plaque. Of most recent import is the involvement of intestinal bacteria that produce trimethylamine, a by-product of carnitine metabolism by microbes in the gut and that is converted to trimethylamine N-oxide (TMAO) in the liver. In animal models, TMAO causes atherosclerosis [98, 98a]. In human models, TMAO increases platelet production and reactivity and the formation of foam cells within plaques. There is also significantly higher relative risk of atherosclerosis in patients with the highest TMAO levels compared with the lowest levels [99].

In human studies of the microbiota/TMAO model, vegans fed carnitine did not have greater TMAO levels, which led researchers to theorize that this population lacks sufficient meat-degrading microbes due to dietary differences (Koeth et al., 2013). While carnitine is found most abundantly in red meat and eggs, other food sources of carnitine include poultry and fish. In studies comparing dietary carnitine sources, consumption of fish high in carnitine was shown to be protective against atherosclerosis, and therefore, carnitine alone cannot be the single high-risk variable in atherosclerosis [99]. Other studies in humans have shown that individuals with impaired renal function

are most at risk for accumulation of TMAO and, therefore, see greater risk of atherosclerosis alongside intestinal microbiome dysbiosis [100].

Bogiatzi et al. [101] found, in a study of 316 at risk patients, that patients with the highest levels of atherosclerotic plaque had higher levels of TMAO compared with those in the lowest plaque group, independent of renal function. This study also stated that no differences between the microbiota of sample and control existed; however, no explanation of microbiome screening was given, nor were data provided on intestinal microbial composition of participants.

Kasselman et al. [102] posit that the intestinal microbiome plays a role in development of atherosclerotic plaques through inflammatory mechanisms originating in the gut, including the activation of NF-κB, which affects gene expression by activating inflammatory immune cells and downstream by-products such as cytokines, nitric oxide synthase (NOS), and leukocyte adhesion. The proposed mechanism of NF-κB relates to the overproduction of metabolites by microbes in the *Bacteroidetes phyla*, which is seen in higher abundance in individuals with obesity and metabolic syndrome. This increased binding of metabolites such as acetate and propionate, SCFAs favored in a *Bacteroidetes*-dominant microbiome type, to TLR-4 stimulates NF-κB, which stimulates production of inflammatory cytokines by adipocytes [103].

DIETARY INFLUENCE

Probiotic Foods

Perhaps, one of the most ubiquitous nutritional trends of the last decade has been the resurgence of interest in probiotics. Both probiotic foods and supplements work through modifying host immune responses and competitive inhibition of pathogens, with indirect benefits to nutrient digestion and absorption [104]. Many health claims are made about the powers of probiotics, but only a few have been substantiated in human or animal trials.

Fermented foods in the human diet have been found to date back at least 9000 years. Humans have fermented everything from fruits and vegetables, dairy, and alcoholic and nonalcoholic beverages [105]. An important distinction is that while all probiotic foods are fermented, not all fermented foods are probiotic. In order to be probiotic, a food or drink must contain live microbial cultures at the time of ingestion. Some fermentation processes do not yield live cultures, such as alcoholic beverages. The most popular traditional ferments found across broad cultures include yogurt, kombucha, sauerkraut, kimchi, and miso.

Probiotic foods have been found to positively influence the intestinal microbiome in both growth of commensal microorganisms and suppression of pathogens. Zou et al. [106] found that probiotic foods and supplements containing *Lactobacillus* species can prevent and even eradicate *Helicobacter pylori* infections, reducing the rates of stomach cancer. Chiu et al. [107] found that a fermented plant extract drink lowered body weight, body fat, and body mass index, while increasing total phenolic compounds in the plasma of individuals. The same drink also reduced total cholesterol and low-density lipoprotein cholesterol (LDL-C). Subjects were found to have increased abundance of *Bifidobacterium* and *Lactobacillus* genus, with reduced abundance of Escherichia coli and Clostridium perfringens. Another study in children using a probiotic drink containing *Lactobacillus casei* found that levels of *Bifidobacterium* and *Lactobacillus* increased, while levels of *Enterobacteriaceae* and *Staphylococcus* decreased [108]. A probiotic drink containing *Bifidobacterium animalis* was shown to potentiate colonic SCFA production and decrease abundance of pathobiont *Bilophila wadsworthia* [109].

Debate exists whether probiotic supplements confer benefit for the same period of time as probiotic foods. Elli et al. [110] suggest that bacteria in fermented foods last about as long as those found in supplements, approximately 5–7 days, based on stool sample collections of study participants. Bezkorovainy [111] suggests probiotic foods may confer more benefit or yield a greater number of surviving microbes due to the presence of naturally existing prebiotic compounds such as fiber and lactose.

Probiotic Supplements

Despite significant research into the field of probiotics, only a limited number of species have been studied in human trials. Most studies use probiotic strains that are dosed at much higher concentrations than what would be found in probiotic foods [112]. Probiotic supplements usually do not have prebiotics included as traditional fermented foods would; however, some findings suggest that prebiotics included with probiotics increase survivability in harsh gastrointestinal conditions [113].

Probiotics are commonly recommended by health-care providers for patients suffering from IBS; however, due to limited training and education of health-care professionals, recommendations vary over a wide range of products, as do the results of the patient. Most probiotics contain either *Lactobacilli* or *Bifidobacteria* or a combination of strains from both genera. A commonly used yeast-based probiotic strain is *Saccharomyces boulardii*.

Table 2 summarizes the most well-studied clinical benefits of probiotics by specific species association based primarily on human studies, but animal studies were noted.

Table 2 Probiotic Microorganisms With Known Clinical Benefits Based on Human Trials

Clinical Associations and Benefits	Probiotic Microorganisms Associated	Source
Antibiotic-associated diarrhea	*Saccharomyces boulardii* *Lactobacillus rhamnosus* LGG *Lactobacillus acidophilus* *Lactobacillus bulgaricus* *Bifidobacterium longum* *Bifidobacterium lactis*	[73, 104, 114]
Celiac disease	*Bifidobacterium breve*	[115, 116]
Clostridium difficile prevention or treatment	*Lactobacillus plantarum* 299V *Saccharomyces boulardii*	[117, 118]
Constipation	*Lactobacillus casei* *Lactobacillus plantarum* *Lactobacillus rhamnosus* LGG *Lactobacillus reuteri* *Bifidobacterium bifidum* *Bifidobacterium lactis* *Bifidobacterium infantis* *Bifidobacterium longum*	[114]
Depression	Multistrain product (*L. acidophilus*, *L. casei*, and *B. bifidum*) Multistrain product (*B. bifidum*, *B. lactis*, *L. acidophilus*, *L. brevis*, *L. casei*, *L. salivarius*, and L. *lactis*) *Lactobacillus helveticus* *Bifidobacterium longum*	[119–121]
Dermatological disorders	*Lactobacillus rhamnosus* LGG *Lactobacillus salivarius*	[114, 122–124]
Fortification of intestinal barrier (reducing permeability)	*Lactobacillus plantarum* 299V *Bifidobacterium*	[68, 117, 125, 126]
Glycemic control	Multispecies supplement (*L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, and *Streptococcus thermophilus*)	[127]
Helicobacter pylori infection reduction	*Bifidobacteria—multiple strains* (*BIR-0304*, *BIR-0307*, *BIR-0312*, *BIR-0324*, *BIR-0326*, *BIR-0349*)	[128]
Inflammatory bowel disease (IBD)—Crohn's disease	*Saccharomyces boulardii* *Bifidobacterium*	[104, 129]
Inflammatory bowel disease (IBD)—ulcerative colitis (UC)	*Saccharomyces boulardii* *Bifidobacterium* VSL#3[a] Multiple strain product (*B. breve*, *B. bifidum*, and *L. acidophilus*)	[104, 130, 130a]
Intestinal hyperpermeability	*Lactobacillus plantarum* *Lactobacillus rhamnosus* LGG *Lactobacillus acidophilus* Multistrain product (*L. acidophilus*, *L. rhamnosus*, *L. casei*, *L. plantarum*, *L. fermentum*, *B. lactis*, *B. breve*, *B. bifidum*, and *S. thermophilus*)	[125, 131, 132]
Irritable bowel syndrome (diarrhea-predominant)	VSL#3[a] *Bifidobacterium longum* spp. *infantis* *Lactobacillus rhamnosus* LGG	[104, 133–135]

Continued

Table 2 Probiotic Microorganisms With Known Clinical Benefits Based on Human Trials *Continued*

Clinical Associations and Benefits	Probiotic Microorganisms Associated	Source
Kidney stones	*Oxalobacter formigenes*	[24]
Nonsteroidal antiinflammatory drug (NSAID) enteropathy	*Lactobacillus acidophilus*	[136]
Obesity	*Lactobacillus gasseri* *Lactobacillus acidophilus*	[114, 137]
Respiratory tract infections	*Lactobacillus rhamnosus* LGG *Lactobacillus plantarum* *Lactobacillus paracasei*	[138, 139]
Rheumatoid arthritis	*Lactobacillus casei* Multiple strain product (*L. acidophilus*, *L. casei*, and *B. bifidum*)	[140, 141]
Seasonal allergies	VSL#3 *Lactobacillus casei* Combination of *L. rhamnosus* LGG + *L. gasseri* *Bifidobacterium longum*	[142]
Travelers' diarrhea	*Lactobacillus rhamnosus* LGG *Saccharomyces boulardii* *Lactobacillus acidophilus* *Lactobacillus casei*	[104, 114]

[a]*VSL#3 is a multistrain probiotic product containing* L. casei, L. plantarum, L. acidophilus, L. bulgaricus, B. longum, B. breve, B. infantis, *and* S. thermophilus.

In addition to the disease- or symptom-specific benefits in Table 2, general benefits of specific probiotic supplements include reduction of inflammation caused by pathogenic or inflammatory microbes [143]; competitive inhibition of pathogens and prevention of pathogenic adhesion to mucosal surfaces [126]; and even contributing to the production and absorption of antioxidants from both diet and endogenous production, such as glutathione [127].

When selecting a probiotic product, consideration should be given to important features such as its colony-forming unit (CFU) count and its ability to deliver live microorganisms to the colon, where they are able to thrive and produce benefit to the host. In vitro studies have claimed that probiotic organisms do not survive digestion [144]; however, microencapsulated or enteric coated products are often more effective than products in standard capsules or powders due to allowing for better survival of extreme pH changes in the upper GI tract [104]. Probiotic supplements can be detected in the stool of the host for about 5–7 days after consumption

and, therefore, must be consumed regularly to provide significant long-term benefit [110, 111]. Some concerns exist as to the contents of probiotic supplements being accurate based on labeling, as some have been found not to contain any live organisms or not contain the organisms listed on their labels [145, 146].

One last category of probiotics of relevance is that of spore-forming bacteria. Currently, only products containing *Bacillus* species are available commercially with spore-forming microorganisms, and some concerns exist about their safety in humans [147]. Limited research available suggests that species without toxin-producing genes are considered safe for human consumption [148]. Several human pathogens exist in the same genus (B. anthracis and B. cereus) but are unrelated to those commonly used in probiotic products (B. subtilis and B. coagulans) [149]. Spore formers are antibiotic-resistant while in their spore form. *Bacillus*, a genus traditionally introduced to humans through soil content or consumption, is more resilient in the human GI tract than nonspore formers due to its ability to survive more extreme pH and temperature [147]. *Bacillus* strains have been reported to display antimicrobial, antioxidative, and immune-modulatory activity in the host, due to their ability to produce AMPs [149].

Prebiotics

Fiber Variety and Diversity

Prebiotics are nutritional components that, when consumed by the host, impart benefit to commensal microbes in the GI tract and increase abundance of one or more of those microbes. Prebiotics can be found in plant sources and come from either fibrous components or phenolic components. Fibrous components of nutrients are not available for digestion by the human host due to a lack of appropriate fiber-degrading enzymes; however, commensal microbes within the host's GI tract possess such enzymes. SCFAs are just one by-product of that microbial digestion, and diets low in fiber and high in animal protein have been shown to decrease the abundance of SCFA (butyrate and acetate) in the colon [17]. Animal studies have also shown that, in addition to balancing the *Firmicutes-Bacteroidetes* ratio, they also dose-dependently increase satiety hormones in the host [150].

The main categories of fiber include fructooligosaccharides (FOS), galactooligosaccharides (GOS), xylooligosaccharides (XOS), resistant starch, and pectin. Each type of fiber has different effects on the microbiome and on the host's metabolism and health, due to differing chemical structures and metabolites of its fermentation.

FOS has a strong stimulatory effect on the abundance of *Bifidobacteria* and on levels of SCFAs found in the colon. This fiber group also increases the abundance of *Lactobacilli* in both the small and large intestines [151, 152]. In addition, the increase in SCFAs appears to reduce plasma levels of free fatty acids (FFA), which not only improves glucose uptake but also influences gut hormones such as GLP-1 and PYY, which influence glycemic control through stimulation of insulin production [151].

GOS also has stimulatory effects on the abundance of *Bifidobacteria* [153] and has been shown to significantly improve clinical outcomes for individuals with reduced lactose digestion and tolerance through increasing abundance of lactose-fermenting *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus* [154]. In addition, GOS has also shown to increase fecal butyrate concentrations [155].

XOS stimulates growth of *Bifidobacteria* [156–158] and has been shown to suppress overgrowths of pathogens in the GI tract [158]. A trial conducted by Van den Abbeele et al. [159] demonstrated that a XOS and green coffee extract blend increased *Bifidobacteria* and *Akkermansia muciniphila*, an important mucus-degrading commensal in the colon, and modulated the intestinal immune system to favor antiinflammatory responses.

Resistant starch (RS) is so named because its molecular structure prevents its digestion by host enzymes; therefore, it is resistant to digestion by the human host, but not by commensal microbes in the colon. RS reduces the abundance of pathogenic *Proteobacteria* such as E. coli/*Shigella* and significantly increases the abundance of *Bifidobacteria*, which increases SCFA levels in the colon [160]. RS also attenuates postprandial (but not fasting) insulin and glucose responses in insulin-resistant individuals, while increasing abundance of *Faecalibacterium*, *Roseburia*, *Akkermansia*, and *Ruminococcus*, which increases colonic SCFAs [84, 161–163].

Major dietary sources of prebiotic fibers are listed in Table 3 to assist in nutritional selection and variety for optimal intake of prebiotic foods.

Of note, prebiotics should be used with caution if one suspects the presence of small intestinal bacterial overgrowth (SIBO), as they may exacerbate overgrowths of microorganisms in the small bowel and contribute to further inflammatory symptoms [165–169].

Phenolic Compounds From Diet and Diversity

Phenolic compounds are chemicals in plants that impart some beneficial action either on the microbiota, which consume or convert them, or on the human host, who absorbs them. Phenolic compounds are usually pigment-associated,

Table 3 Sources of Prebiotic Fibers From Diet

Type of Fiber	Food Sources
Fructooligosaccharides (FOS) (primarily feed *Lactobacillus* and *Bifidobacteria*)	Chicory root, agave, bananas, inulin (onions, leeks, and garlic), asparagus, wheat, barley, nuts
Galactooligosaccharides (GOS) (primarily feed *Lactobacillus* and *Bifidobacteria*) [153]	Jerusalem artichokes, black beans, kidney beans, lima beans, beet roots, broccoli, chickpeas, lentils
Xylooligosaccharides (XOS) (primarily feed *Lactobacillus* and *Bifidobacteria*)	Milk, honey, vegetables with a high cellulose content (celery, Brussels sprouts, cabbage, kale, squash, and sprouts), rice bran, soybeans, bamboo shoots
Resistant starch (can be fermented to yield butyrate) [161]	Banana flour, cooked oats, lentils, green bananas, white beans, barley, green peas, whole wheat, nuts
Pectin (can be fermented to yield butyrate and increases intestinal epithelial cell proliferation [164])	Apples, pears, guavas, citrus fruits, plums, gooseberries

and the amount and diversity of them differ by the hue of the plant, the quality of the soil in which the plant grows, and factors such as the environmental conditions under which the plant is grown [170].

The chemical structure of phenolic compounds is what classifies each compound. The main mechanisms of benefit in the gastrointestinal tract appear to be the stimulation of growth of commensal microbes and the antimicrobial properties of phenolic compounds toward pathobiont and pathogenic microorganisms [171].

The most commonly used and potent antimicrobial phenolic compounds are presented in Table 4.

Phenolic compounds are known to ameliorate inflammation through a variety of pathways, including locally reducing oxidative stress in the intestinal tract; altering gene expression related to inflammatory response, which includes NF-κB; and suppression of downstream cytokine responses [182].

Microbes in the gastrointestinal tract act on phenolic compounds by performing deglycosylation, the hydrolysis of esters and amides, and deglucuronidation of excreted mammalian metabolites; aromatic dehydroxylation, demethoxylation, and demethylation; and hydrogenation, α-oxidation, and β-oxidation [189].

There exists some debate as to whether the majority of phenolic compounds are even available to the host, due to limited absorption in the gastrointestinal tract. Williamson and Clifford [189] suggest that there is some partial absorption of most phenolic compounds, while Kahle et al. [190] found that around 20% of phenolic compounds are absorbed by the host in the small intestine,

Table 4 Most Commonly Used and Potent Phenolic Compounds From Nutritional Sources

Plant Source/Phenolic Compound	Microbes Impacted	Main Attributes
Berberine (found most abundantly in goldenseal, Oregon grape, barberry, and Chinese goldthread plants)	Gram-negative microbes producing LPS	Improves intestinal barrier integrity in rats with endotoxemia (LPS); injections of LPS inhibited the expression of TJ proteins but was attenuated by berberine administration [172]
	Staphylococcus aureus	Berberine contains a weak acid that inhibits bacterial defenses against berberine alkaloids and enhances the antimicrobial properties of the polyphenol against S. aureus [173]
	Escherichia coli, Bacillus subtilis, S. *aureus*, and Enterococcus faecalis (methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE))	Inhibition of both gram-positive and gram-negative bacteria [171]
	Decreases *Firmicutes* and increases *B. phyla*, reducing overall ratio; decrease in *Ruminococcus* species	Berberine is an alkaloid and considered an "antibiotic with broad spectrum" [174]
Carvacrol (from oregano)	*Escherichia coli* O157:H7, *Salmonella typhimurium*, Listeria monocytogenes	Inhibition of pathogenic microorganisms [171]
	Mycobacterium tuberculosis, *S. aureus*, L. monocytogenes, E. coli, E. faecium, *S. enterica*, Pseudomonas aeruginosa	Inhibition of pathogenic microorganisms [171]
	Bacillus subtilis	Effective antimicrobial against soil-based bacteria [175]
	Klebsiella oxytoca, K. pneumoniae, *E. coli*	Inhibits pathogenic microorganisms [176]
	Enterohemorrhagic *E. coli* O157:H7 (EHEC)	Reduces EHEC motility and attachment to human intestinal epithelial cells and decreased Shiga-like toxin synthesis [177]
Thymol (from thyme)	*Salmonella typhimurium*, *L. monocytogenes*, *M. tuberculosis*	Inhibition of pathogenic microorganisms [171]
	Escherichia coli, *K. pneumoniae*, methicillin-resistant *S. aureus* (MRSA); extremely strong activity against 120 strains of *Staphylococcus*, *Enterococcus*, *Escherichia*, and *P. genera*	Inhibits growth of pathogenic microorganisms [178]
	Klebsiella oxytoca, *K. pneumoniae*, *E. coli*	Inhibits pathogenic microorganisms [176]
	Enterohemorrhagic *E. coli* O157:H7 (EHEC)	Reduces EHEC motility and attachment to human intestinal epithelial cells and decreased Shiga-like toxin synthesis [177]

Table 4 Most Commonly Used and Potent Phenolic Compounds From Nutritional Sources *Continued*

Plant Source/Phenolic Compound	Microbes Impacted	Main Attributes
Cinnamic acid and cinnamaldehyde (from cinnamon)	*Mycobacterium tuberculosis*, *E. coli O157:H7*, *S. typhimurium*, *L. monocytogenes*	Inhibit growth of pathogenic microorganisms [171]
	Pseudomonas aeruginosa	Strongly inhibit pathogenic microorganisms [179]
	Enterohemorrhagic *E. coli* O157:H7 (EHEC)	Reduce EHEC motility and attachment to human intestinal epithelial cells and decreased Shiga-like toxin synthesis [177]
Resveratrol (most concentrated in red wine)	*Helicobacter pylori*	May reduce abundance of pathogen and inflammation resulting in gastritis [180]
	Bifidobacteria, *Akkermansia*	Promotes abundance of commensal microorganisms [174]
	Enterococcus, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *B. uniformis*, *Eggerthella lenta*, and *Blautia coccoides*, *Eubacterium rectale*	Daily consumption of red wine polyphenols for 4 weeks significantly increased commensal microorganisms [181]
	Vibrio cholerae, Proteus mirabilis	Inhibits growth of pathogenic microorganisms [171]
	Gram-negative LPS-producing bacteria	Reduces abundance of endotoxin-producing microorganisms [182]
Curcumin (from turmeric)	Decrease in *Enterobacteria* and Enterococci, increase in *Lactobacillus* and *Bifidobacterium*	Animal study: decreases abundance of pathogenic and pathobiont taxa and reduces translocation of microbes and endotoxins through intestinal epithelial barrier into systemic circulation [183]
	Increased the abundance of butyrate-producing bacteria	Animal study: suppression of NF-κB activation in colonic epithelial cells, increased fecal butyrate level, increased expansion of Treg cells regulatory dendritic cells [184]
	Reduction in *Prevotella*; significant increase in *Alistipes*; abundance of *Bacteroides* was significantly higher; *Lactobacillus* increased, *Ruminococcus* decreased	Animal study: significant beneficial effects on increases in *Lactobacillus*, and reducing *Firmicutes*-to-*Bacteroidetes* ratio and reducing abundance of opportunists [185]
	Nonpathogenic *E. coli*, may stimulate growth of beneficial strains	Exhibits the highest curcumin-converting ability [186]
Catechins/epigallocatechins (EGCG) (from tea)	*Helicobacter pylori* and *E. coli*	Inhibits growth of pathogenic microorganisms [187]
Quercetin	*Escherichia coli*, *Serratia*, and *K. pneumoniae*	Inhibits growth of pathogenic microorganisms [188]
	Bacteroides vulgatus, *A. muciniphila*	Increased abundance of commensal microorganisms [174]

while the majority arrive in tact in the colon and are degraded by colonic microbes, stimulating growth of certain taxa.

Examples of those phenolic compounds that stimulate growth of beneficial bacteria include hydroxycinnamic acid and chlorogenic acid in coffee (both also found in fruits), which stimulate butyrate producers in the colon [191], and anthocyanins in blueberries and other blue, purple, and red produce that have shown stimulatory effects on the growth of commensal microorganisms such as *Bifidobacteria* and *Akkermansia* [192, 193].

Thousands of plant-based phenolic compounds exist in the human diet, and the most optimal intake of those compounds will be a diet inclusive of a high degree of variety from plant sources. Table 5 lists 50 of the highest phenolic content foods commonly consumed in the human diet with the most prevalent phenolic compounds found in those foods.

ADDITIONAL BENEFICIAL NUTRIENTS

Beyond probiotics, prebiotics, and phenolic compounds, other micronutrients common to the human diet impart benefit to both the microbiota and the host. Table 6 lists and describes the most well studied of those, which include the fat-soluble vitamins A and D, omega-3 fatty acids, and the amino acid L-glutamine. All of these nutrients also impart benefit to the intestinal epithelial barrier through actions of immunomodulation and/or tight junction modulation [34, 84, 195, 196, 198, 203, 205, 210, 213, 214].

CONCLUSION

While the intestinal microbiome obviously holds influence over broad health functions in the host, there is still much to be studied in regard to its role in disease. Technological advances have allowed for more accurate sequencing of the microbiome and accelerated speed and reach of research, which have allowed for greater understanding of how the human microbiome differs from animal models in studies. The functions of the gut microbiome in human health and disease include immunomodulation, fiber fermentation, vitamin and nutrient metabolism, inflammatory response modulation, competitive inhibition of pathogens, and mucosal barrier fortification.

Communication between the microbiota and the human host is bidirectional and takes place via chemical messages from metabolites such as SCFAs, AMPs, and microbial membrane peptides. Of key importance to this communication is the diversity and abundance of species, which are affected by a number of

Table 5 Commonly Consumed High-Polyphenol Foods and Drinks by Phenolic Content and Associated Phenolic Compounds

	Food	Major Phenolic Compounds Found		Food	Major Phenolic Compounds Found
1	Cilantro	Caffeic acid, protocatechuic acid, glycitin, and vanillic acid [194]	26	Roasted soybean seed	Isoflavonoids: daidzein, glycitein, genistein, and glucosides
2	Cloves (spice)	Hydroxyhenylpropenes: eugenol, acetyl eugenol	27	Milk chocolate	Flavanols: EC
3	Peppermint, dried (herb)	Flavonoids, eriocitrin; hydroxycinnamic acids, rosmarinic acid	28	Strawberry	Anthocyanins, flavanols, hydroxybenzoic acids, hydroxycinnamic acids, stilbenes
4	Celery seed	Apigenin, luteolin	29	Red raspberry	Anthocyanins, flavonols, hydroxycinnamic acids
5	Cocoa powder	Flavanols: epicatechin (EC)	30	Coffee	Phenolic acids: chlorogenic acid
6	Mexican oregano, dried (herb)	Dihydroquercetin; naringenin; luteolin; flavonols: galangin, quercetin	31	Ginger, dried (root)	Hydroxycinnamic acids, other: hydroxyphenylpropenes
7	Dark chocolate (70% or higher)	Flavanols, epicatechin (EC); hydroxycinnamic acid, ferulic acid	32	Whole grain wheat flour	Phenolic acids: hydroxybenzoic acids, hydroxycinnamic acids
8	Flaxseed meal	Hydroxycinnamic acids, lignans	33	Prune	Flavonols, hydroxycinnamic acids
9	Black elderberry	Anthocyanins; flavonols: quercetin	34	Almond	Flavonols: kaempferol, quercetin, hydroxybenzoic acids
10	Chestnut	Hydroxybenzoic acids: gallic acid, ellagic acid, tannins	35	Black grape	Anthocyanins, flavanols, stilbenes
11	Sage, dried (herb)	Hydroxybenzoic acids: gallic acid, vanillic acid; hydroxycinnamic acids: caffeic acid, rosmarinic acid	36	Red onion	Anthocyanins, flavonols
12	Rosemary, dried (herb)	Flavonols; hydroxycinnamic acids: rosmarinic acid, caffeic acid	37	Thyme, fresh (herb)	Flavones; hydroxycinnamic acids: rosmarinic acid, caffeic acid
13	Thyme, dried (herb)	Hydroxybenzoic acids; hydroxycinnamic acids, rosmarinic acid	38	Refined maize flour	Hydroxycinnamic acids
14	Blueberry	Anthocyanins; flavonols, quercetin; phenolic acids, chlorogenic acid	39	Soy, tempeh	Isoflavonoids: daidzein, glycitein, genistein, and glucosides
15	Capers (herb/seasoning)	Flavonols, kaempferol; quercetin	40	Whole grain rye flour	Alkylphenols
16	Curcumin	Curcuminoids, flavonoids, phenolic acids	41	Apple	Phlorizin; phenolic acids: chlorogenic acid, quercetin

Continued

Table 5 Commonly Consumed High-Polyphenol Foods and Drinks by Phenolic Content and Associated Phenolic Compounds *Continued*

	Food	Major Phenolic Compounds Found		Food	Major Phenolic Compounds Found
17	Black olive	Anthocyanins; flavones, luteolin; flavonols; hydroxycinnamic acids; tyrosols: hydroxytyrosol, oleuropein	42	Spinach	Flavonols
18	Hazelnut	Flavonols: epigallocatechin (EGCG)	43	Black tea	Flavanols: catechin, EGCG, procyanidin; flavonols: kaempferol, quercetin; hydroxybenzoic acids
19	Pecan nut	Flavonols: catechin, EGCG	44	Red wine	Phenolic acids, anthocyanins, tannins, stilbenes (resveratrol)
20	Plum	Phenolic acids: chlorogenic acid; procyanidins, anthocyanins	45	Green tea	Flavanols: EC, EGCG
21	Green olive	Hydroxycinnamic acids; tyrosols, oleuropein	46	Yellow onion	Flavonols: quercetin
22	Sweet basil, dried (herb)	Hydroxycinnamic acids	47	Pure apple juice	Dihydrochalcones; flavanols: catechin, procyanidin; flavonols: kaempferol, quercetin; hydroxycinnamic acids
23	Curry powder (spice)	Curcuminoids	48	Pure pomegranate juice	Punicalagin (an ellagitannin)
24	Sweet cherry	Anthocyanins, flavonols, hydroxycinnamic acids	49	Extra virgin olive oil	Tyrosols, lignans: pinoresinol; phenolic acids, hydrolysable tannins
25	Blackberry	Anthocyanins; flavanols, EC; phenolic acid, ellagic acid	50	Peaches (whole, including peel)	Flavanols, catechin; hydroxycinnamic acids

Data reproduced from (unless noted otherwise) Phenol Explorer. Rothwell JA, Pérez-Jiménez J, Neveu V, Medina-Ramon A, M'Hiri N, Garcia Lobato P, Manach C, Knox K, Eisner R, Wishart D, Scalbert A. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database 2013. https://doi.org/10.1093/database/bat070.

influences from birth through adulthood, including environmental exposures and the use of antibiotics. Low diversity is associated with a number of chronic diseases in humans. Restoring balance to this ecosystem therapeutically is possible through a combination of prebiotic foods, probiotic foods and supplements, and plants high in phenolic compounds.

Table 6 Additional Beneficial Nutrients With Immune and Microbial Modulatory Properties

Nutrient	Associations With Immunity	Associations With Microbiota
Vitamin A	Dietary intake of fiber can alter the populations of SCFA-producing microbes favoring growth of *Lactobacillus* genus, *Bacteroidetes* phylum, and Akkermansia genus [84]	Retinoic acid/vitamin A levels are associated with amelioration of pathogen inflammation and increased levels of zonulin (ZO-1) and occludin proteins into the cellular tight junctions [195]
	The conversion of vitamin A to retinoic acid, its active form, influences dendritic cell communication with T cells to increase differentiation into Tregs. Without adequate levels of retinoic acid, tolerogenic dendritic cells have reduced T-cell differentiation [84]	
	Retinoic acid influences dendritic cell signaling to promote Treg production [34]	
	Trans-retinoic acid prevents the overconversion of T cells into Th-like cells, which can lead to autoimmunity; adequate retinoic acid selects for Treg production and reduces autoimmune responses [196]	
Vitamin D	Vitamin D influences both FOXp3- and IL-10-producing Tregs and inhibits Th17 pro-inflammatory pathways [34]	5000 IU of vitamin D3 per day for 90 days increased the abundance of *Akkermansia*, which promotes immune tolerance and increased butyrate producers *Faecalibacterium* and *Coprococcus* [197]
	Defensins are produced within human macrophages and dendritic cells, influenced by vitamin D; vitamin D induces host response to microbes [198]	Vitamin D3 treatment caused beneficial changes in *Firmicutes, Actinobacteria, and Proteobacteria* levels in MS patients and an increase in *Enterobacteria* [199]
	Vitamin D stimulates production of pattern recognition receptors, antimicrobial peptides, and cytokines and affects microbe sensing and inhibition of pathogens [198]	Animal study showed that high-dose vitamin D3 supplementation is associated with a shift to a more inflammatory fecal microbiome and increased susceptibility to colitis in animals with genetic predisposition to colitis, with a fall in circulating vitamin D occurring as a secondary event in response to the inflammatory process [200]
		Vitamin D deficiency changes the intestinal microbiome and reduces microbial B vitamin production in the gut. A lack of pantothenic acid results and produces a pro-inflammatory state [201]
		Vitamin D3 supplementation changed the gut microbiome in the upper GI tract to a less inflammatory state [202]
Omega-3 fatty acids	Eicosapentaenoic acid reinforces cellular tight junctions [203]	Higher omega-3 (specifically DHA) intake is highly correlated with microbiome diversity [204]
		Increase is seen in butyrate-producing *Lachnospiracea* species: *Eubacterium,*

Continued

Table 6 Additional Beneficial Nutrients With Immune and Microbial Modulatory Properties *Continued*

Nutrient	Associations With Immunity	Associations With Microbiota
	An in vitro study found that omega-3s alone decreased epithelial permeability and improved tight junction stability [205]	*Roseburia, Anaerostipes*, and *Coprococcus* [206]
		Essential fatty acid double bonds being hydrolyzed in the large intestine has antimicrobial properties and increases *Bifidobacteria* while decreasing intestinal permeability [206]
		Omega-3s from plant sources may lower *Bacteroidetes*; in an animal study, a significant decrease in the proportion of phylum *Bacteroidetes* species was observed; a saturated fatty acid-rich diet group showed a significantly greater decrease in *Bacteroidetes* proportion (resulting in a higher *Firmicutes*-to-*Bacteroidetes* ratio) [207]
		In an animal study, fish sources rich in omega-3 fatty acids appear to bring *Firmicutes*-to-*Bacteroidetes* ratio back into balance [208]
		Omega-3 fatty acids decreased *Firmicutes*-to-*Bacteroidetes* ratio [209]
L-Glutamine	An animal study in rats suggests that glutamine alone, but not glutamine with arginine, improves intestinal barrier permeability that resulted from chemotherapy [210]	After 14 days of supplementation, subjects in the glutamine group had significant differences in the *Firmicutes* and *Actinobacteria* phyla compared with those in the control group [211]
	In vitro glutamine and arginine supplementation improve methotrexate-induced barrier permeability [212]	
	Glutamine is used by rapidly dividing epithelial cells, enhances expression of tight junction protein genes and production of tight junction proteins to fortify the barrier [213]	
	Glutamine supplementation resulted in increased secretory IgA (SIgA) and a shift in the *Firmicutes*-to-*Bacteroidetes* ratio to favor *Bacteroidetes* in the ileum and increased the abundance of *Streptococcus* and *Bifidobacterium* in the jejunum [214]	

References

[1] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett C, Knight R, Gordon JI. The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature 2007;449(7164):804–10. https://doi.org/10.1038/nature06244.

[2] Weinstock GM. Genomic approaches to studying the human microbiota. Nature 2012;489(7415):250–6. https://doi.org/10.1038/nature11553.

[3] Olsen GJ, Lane DJ, Giovannoni SJ, Pace NR, Stahl DA. Microbial ecology and evolution: a ribosomal RNA approach. Annu Rev Microbiol 1986;40(1):337–65. https://doi.org/10.1146/annurev.mi.40.100186.002005.

[4] Mysara M, Vandamme P, Props R, Kerckhof F-M, Leys N, Boon N, Monsieurs P. Reconciliation between operational taxonomic units and species boundaries. FEMS Microbiol Ecol 2017;93(4):fix029. https://doi.org/10.1093/femsec/fix029.

[5] Rampelli S, Turroni S. From whole-genome shotgun sequencing to viral community profiling: the ViromeScan tool. In: Pantaleo V, Chiumenti M, editors. Viral metagenomics. Methods in molecular biology. vol. 1746. New York, NY: Humana Press; 2018.

[6] Gupta RS. Protein phylogenies and signature sequences: a reappraisal of evolutionary relationships among archaebacteria, eubacteria, and eukaryotes. Microbiol Mol Biol Rev 1998;62(4):1435–91.

[7] Wang Y, Tian RM, Gao ZM, Bougouffa S, Qian P. Optimal eukaryotic 18S and universal 16S/18S ribosomal RNA primers and their application in a study of symbiosis. PLoS ONE 2014;9(3). https://doi.org/10.1371/journal.pone.0090053.

[8] Bashiardes S, Zilberman-Schapira G, Elinav E. Use of metatranscriptomics in microbiome research. Bioinform Biol Insights 2016;2016(10):19–25. https://doi.org/10.4137/BBI.S34610.

[9] Lee PY, Chin S, Neoh H, Jamal R. Metaproteomic analysis of human gut microbiota: where are we heading? J Biomed Sci 2017;24(1):1–8. https://doi.org/10.1186/s12929-017-0342-z.

[10] Hofer U. Microbiome: precision engineering of gut metabolites. Nat Rev Microbiol 2017;16(1):2–3. https://doi.org/10.1038/nrmicro.2017.159.

[11] Fábián T, Fejérdy P, Csermely P. Salivary genomics, transcriptomics and proteomics: the emerging concept of the oral ecosystem and their use in the early diagnosis of cancer and other diseases. Curr Genomics 2008;9(1):11–21. https://doi.org/10.2174/138920208783884900.

[12] Mändar R, Punab M, Borovkova N, Lapp E, Kiiker R, Korrovits P, Truu J. Complementary seminovaginal microbiome in couples. Res Microbiol 2015;166(5):440–7. https://doi.org/10.1016/j.resmic.2015.03.009.

[13] Javurek AB, Spollen WG, Ali AMM, Johnson SA, Lubahn DB, Bivens NJ, Rosenfeld CS. Discovery of a novel seminal fluid microbiome and influence of estrogen receptor alpha genetic status. Sci Rep 2016;6(1):23027. https://doi.org/10.1038/srep23027.

[14] Shapiro H, Thaiss CA, Levy M, Elinav E. The cross talk between microbiota and the immune system: metabolites take center stage. Curr Opin Immunol 2014;30:54–62. https://doi.org/10.1016/j.coi.2014.07.003.

[15] Sharon G, Garg N, Debelius J, Knight R, Dorrestein P, Mazmanian S. Specialized metabolites from the microbiome in health and disease. Cell Metab 2014;20(5):719–30. https://doi.org/10.1016/j.cmet.2014.10.016.

[16] Belenguer A, Duncan SH, Calder AG, Holtrop G, Louis P, Lobley GE, Flint HJ. Two routes of metabolic cross-feeding between *Bifidobacterium adolescentis* and butyrate-producing anaerobes from the human gut. Appl Environ Microbiol 2006;72(5):3593–9. https://doi.org/10.1128/AEM.72.5.3593-3599.2006.

[17] Levy R, Borenstein E. Metagenomic systems biology and metabolic modeling of the human microbiome: from species composition to community assembly rules. Gut Microbes 2014;5(2):265–70. https://doi.org/10.4161/gmic.28261.

[18] Rossi M, Amaretti A, Raimondi S. Folate production by probiotic bacteria. Nutrients 2011;3(1):118–34. https://doi.org/10.3390/nu3010118.

[19] Sato T, Yamada Y, Ohtani Y, Mitsui N, Murasawa H, Araki S. Production of menaquinone (vitamin K 2)-7 by Bacillus subtilis. J Biosci Bioeng 2001;91(1):16–20. https://doi.org/10.1016/S1389-1723(01)80104-3.

[20] Degnan PH, Taga ME, Goodman AL. Vitamin B12 as a modulator of gut microbial ecology. Cell Metab 2014;20(5):769–78. https://doi.org/10.1016/j.cmet.2014.10.002.

[21] Magnúsdóttir S, Ravcheev D, de Crécy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Front Genet 2015;6:148. https://doi.org/10.3389/fgene.2015.00148.

[22] Mehta M, Goldfarb DS, Nazzal L. The role of the microbiome in kidney stone formation. Int J Surg 2016;https://doi.org/10.1016/j.ijsu.2016.11.024.

[23] Sadaf H, Raza SI, Hassan SW. Role of gut microbiota against calcium oxalate. Microb Pathog 2017;109:287–91. https://doi.org/10.1016/j.micpath.2017.06.009.

[24] Sikora P, Niedźwiadek J, Mazur E, Paluch-Oleś J, Zajączkowska M, Kozioł-Montewka M. Intestinal colonization with oxalobacter formigenes and its relation to urinary oxalate excretion in pediatric patients with idiopathic calcium urolithiasis. Arch Med Res 2009;40(5):369–73. https://doi.org/10.1016/j.arcmed.2009.05.004.

[25] Parks OB, Pociask DA, Hodzic Z, Kolls JK, Good M. Interleukin-22 signaling in the regulation of intestinal health and disease. Front Cell Dev Biol 2015;3:85.

[26] Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016;535(7610):65–74. https://doi.org/10.1038/nature18847.

[27] Ege MJ, Mayer M, Normand A, Genuneit J, Cookson WOCM, Braun-Fahrländer C, GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364(8):701–9. https://doi.org/10.1056/NEJMoa1007302.

[28] Neu J, Rushing J. Cesarean versus vaginal delivery: long term infant outcomes and the hygiene hypothesis. Clin Perinatol 2011;38(2):321–31. https://doi.org/10.1016/j.clp.2011.03.008.

[29] von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. Nat Rev Immunol 2010;10(12):861–8. https://doi.org/10.1038/nri2871.

[30] Umu ÖCO, Rudi K, Diep DB. Modulation of the gut microbiota by prebiotic fibres and bacteriocins. Microb Ecol Health Dis 2017;28(1). https://doi.org/10.1080/16512235.2017.1348886. 1348886-11.

[31] Noble EE, Hsu TM, Kanoski SE. Gut to brain dysbiosis: mechanisms linking western diet consumption, the microbiome, and cognitive impairment. Front Behav Neurosci 2017;11. https://doi.org/10.3389/fnbeh.2017.00009.

[32] Riordan S, McIver C, Thomas D, Dunscombe V, Bolin T, Thomas M. Luminal bacteria and small-intestinal permeability. Scand J Gastroenterol 1997;32:556–63.

[33] Bollrath J, Powrie FM. Controlling the frontier: regulatory T-cells and intestinal homeostasis. Semin Immunol 2013;25(5):352–7. https://doi.org/10.1016/j.smim.2013.09.002.

[34] Hoeppli RE, Wu D, Cook L, Levings MK. The environment of regulatory T cell biology: cytokines, metabolites, and the microbiome. Front Immunol 2015;6:61. https://doi.org/10.3389/fimmu.2015.00061.

[35] Warshakoon HJ, Burns MR, David SA. Structure-activity relationships of antimicrobial and lipoteichoic acid-sequestering properties in polyamine sulfonamides. Antimicrob Agents Chemother 2009;53(1):57–62. https://doi.org/10.1128/AAC.00812-08.

[36] Maurice C, Haiser H, Turnbaugh P. Xenobiotics shape the physiology and gene expression of the active human gut microbiome. Cell 2013;152(1–2):39–50. https://doi.org/10.1016/j.cell.2012.10.052.

[37] Hsiao E, McBride S, Hsien S, Sharon G, Hyde E, McCue T, Mazmanian S. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 2013;155(7):1451–63. https://doi.org/10.1016/j.cell.2013.11.024.

[38] Said HM. Intestinal absorption of water-soluble vitamins in health and disease. Biochem J 2011;437(3):357–72. https://doi.org/10.1042/BJ20110326.

[39] Havenaar R. Intestinal health functions of colonic microbial metabolites: a review. Benefic Microbes 2011;2(2):103–14. https://doi.org/10.3920/BM2011.0003.

[40] Waldecker M, Kautenburger T, Daumann H, Busch C, Schrenk D. Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. J Nutr Biochem 2008;19(9):587–93. https://doi.org/10.1016/j.jnutbio.2007.08.002.

[41] Ostaff MJ, Stange EF, Wehkamp J. Antimicrobial peptides and gut microbiota in homeostasis and pathology. EMBO Mol Med 2013;5(10):1465–83. https://doi.org/10.1002/emmm.201201773.

[42] Zhang L, Gallo R. Antimicrobial peptides. Curr Biol 2015;0960-9822. 26(1):R14–9. https://doi.org/10.1016/j.cub.2015.11.017.

[43] Guo S, Al-Sadi R, Said HM, Ma TY. Lipopolysaccharide causes an increase in intestinal tight junction permeability in vitro and in vivo by inducing enterocyte membrane expression and localization of TLR-4 and CD14. Am J Pathol 2013;182(2):375–87. https://doi.org/10.1016/j.ajpath.2012.10.014.

[44] Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes 2008;57(6):1470–81. https://doi.org/10.2337/db07-1403-1403.

[45] Monte S, Caruana J, Ghanim H, Sia CL, Korzeniewski K, Schentag J, Dandona P. Reduction in endotoxemia, oxidative and inflammatory stress, and insulin resistance after Roux-en-Y gastric bypass surgery in patients with morbid obesity and type 2 diabetes mellitus. Surgery 2012;151(4):587–93. https://doi.org/10.1016/j.surg.2011.09.038.

[46] Huang Z, Kraus VB. Does lipopolysaccharide-mediated inflammation have a role in OA? Nat Rev Rheumatol 2016;12(2):123–9. https://doi.org/10.1038/nrrheum.2015.158.

[47] Jeong H-K, Jou I, Joe E. Systemic LPS administration induces brain inflammation but not dopaminergic neuronal death in the substantia nigra. Exp Mol Med 2010;42(12):823–32. https://doi.org/10.3858/emm.2010.42.12.085.

[48] Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong J-S, Crews FT. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 2007;55(5):453–62. https://doi.org/10.1002/glia.20467.

[49] Ginsburg I. Role of lipoteichoic acid in infection and inflammation. Lancet Infect Dis 2002;2(3):171–9. https://doi.org/10.1016/S1473-3099(02)00226-8.

[50] Gong D, Gong X, Wang L, Yu X, Dong Q. Involvement of reduced microbial diversity in inflammatory bowel disease. Gastroenterol Res Pract 2016;2016:1–7. https://doi.org/10.1155/2016/6951091.

[51] Carroll IM, Ringel-Kulka T, Siddle JP, Ringel Y. Alterations in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Neurogastroenterol Motil 2012;24:521–30. https://doi.org/10.1111/j.1365-2982.2012.01891.x.

[52] Ahn J, Sinha R, Pei Z, Dominianni C, Goedert JJ, Hayes RB, Yang L. Abstract 2290: Human gut microbiome and risk of colorectal cancer, a case-control study. Cancer Res 2013;73(8 Suppl):2290. https://doi.org/10.1158/1538-7445.AM2013-2290.

[53] Schippa S, Iebba V, Barbato M, Di Nardo G, Totino V, Checchi MP, Conte MP. A distinctive "microbial signature" in celiac pediatric patients. BMC Microbiol 2010;10:175. https://doi.org/10.1186/1471-2180-10-175.

[54] Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Gordon JI. A core gut microbiome in obese and lean twins. Nature 2009;457(7228):480–4. https://doi.org/10.1038/nature07540.

[55] Kang D-W, Park JG, Ilhan ZE, Wallstrom G, LaBaer J, Adams JB, Krajmalnik-Brown R. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. PLoS ONE 2013;8(7). https://doi.org/10.1371/journal.pone.0068322.

[56] Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. Clin Exp Allergy 2014;44:842–50. https://doi.org/10.1111/cea.12253.

[57] De Goffau MC, Luopajärvi K, Knip M, Ilonen J, Ruohtula T, Härkönen T, Vaarala O. Fecal microbiota composition differs between children with β-cell autoimmunity and those without. Diabetes 2013;62(4):1238–44. https://doi.org/10.2337/db12-0526.

[58] Wang M, Karlsson C, Olsson C, Adlerberth I, Wold AE, Strachan DP, Institutionen för kliniska vetenskaper, sektionen för kvinnors och barns hälsa. Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol 2008;121(1):129–34. https://doi.org/10.1016/j.jaci.2007.09.011.

[59] Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature 2016;529(7585):212–5. https://doi.org/10.1038/nature16504.

[60] Trosvik P, de Muinck EJ. Ecology of bacteria in the human gastrointestinal tract—identification of keystone and foundation taxa. Microbiome 2015;3. https://doi.org/10.1186/s40168-015-0107-4.

[61] Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Ley RE. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci U S A 2011;108(Suppl. 1):4578–85. https://doi.org/10.1073/pnas.1000081107.

[62] Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. Gut 2004;53(9):1388–9. https://doi.org/10.1136/gut.2004.041640.

[63] Palmer C, Bik E, DiGiulio D, Relman D, Brown P. Development of the human infant intestinal microbiota. PLoS Biol 2007;5:e177. https://doi.org/10.1371/journal.pbio.0050177.

[64] Soto A, Martín V, Jiménez E, Mader I, Rodríguez JM, Fernández L. Lactobacilli and Bifidobacteria in human breast milk: influence of antibiotherapy and other host and clinical factors. J Pediatr Gastroenterol Nutr 2014;59(1):78–88. https://doi.org/10.1097/MPG.0000000000000347.

[65] Correale J, Farez MF. The impact of parasite infections on the course of multiple sclerosis. J Neuroimmunol 2011;233(1):6–11. https://doi.org/10.1016/j.jneuroim.2011.01.002.

[66] Strachan DP. Hay fever, hygiene, and household size. Br Med J 1989;299(6710):1259–60.

[67] Moens F, Verce M, De Vuyst L. Lactate- and acetate-based cross-feeding interactions between selected strains of lactobacilli, bifidobacteria and colon bacteria in the presence of inulin-type fructans. Int J Food Microbiol 2017;241:225–36. https://doi.org/10.1016/j.ijfoodmicro.2016.10.019.

[68] Bottacini F, Ventura M, van Sinderen D, Motherway MO. Diversity, ecology and intestinal function of bifidobacteria. Microb Cell Fact 2014;13. https://doi.org/10.1186/1475-2859-13-S1-S4.

[69] Edelsberg J, Weycker D, Barron R, Li X, Wu H, Oster G, Weber DJ. Prevalence of antibiotic resistance in US hospitals. Diagn Microbiol Infect Dis 2014;78(3):255–62. https://doi.org/10.1016/j.diagmicrobio.2013.11.011.

[70] Lautenbach E, Synnestvedt M, Weiner M, Bilker W, Vo L, Schein J, Kim M. Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. Infect Control Hosp Epidemiol 2009;30(12):1186–92. https://doi.org/10.1086/648450.

[71] Johnston BC, Goldenberg JZ, Vandvik PO, Sun X, Guyatt GH. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 2011;11.

[72] Jakobsson HE, Jernberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS ONE 2010;5(3). https://doi.org/10.1371/journal.pone.0009836.

[73] Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics (Basel, Switzerland) 2017;6(4):21. https://doi.org/10.3390/antibiotics6040021.

[74] Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 2015;12. https://doi.org/10.1002/14651858.CD004827.pub4.

[75] Xu H, Jiang R, Sheng H. Meta-analysis of the effects of bifidobacterium preparations for the prevention and treatment of pediatric antibiotic-associated diarrhea in China. Complement Ther Med 2017;33:105–13. https://doi.org/10.1016/j.ctim.2017.07.001.

[76] Panda S, El khader I, Casellas F, López Vivancos J, García Cors M, Santiago A, Manichanh C. Short-term effect of antibiotics on human gut microbiota. PLoS ONE 2014;9(4):e95476. https://doi.org/10.1371/journal.pone.0095476.

[77] Pérez-Cobas AE, Gosalbes MJ, Frieichs A, Knecht H, Martins Dos Santos VAP. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. Gut 2013;62(11):1591–601. https://doi.org/10.1136/gutjnl-2012-303184.

[78] Koliada A, Syzenko G, Moseiko V, Budovska L, Puchkov K, Perederiy V, Vaiserman A. Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. BMC Microbiol 2017;17. https://doi.org/10.1186/s12866-017-1027-1.

[79] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature 2006;444(7122):1022–3. https://doi.org/10.1038/4441022a.

[80] Lange K, Buerger M, Stallmach A, Bruns T. Effects of antibiotics on gut microbiota. Dig Dis 2016;34(3):260–8. https://doi.org/10.1159/000443360.

[81] Kinoshita M, Suzuki Y, Saito Y. Butyrate reduces colonic paracellular permeability by enhancing PPARγ activation. Biochem Biophys Res Commun 2002;293(2):827–31. https://doi.org/10.1016/S0006-291X(02)00294-2.

[82] National Institutes of Health. Colorectal cancer fact sheet. Retrieved from, https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=84; 2018. Accessed 1 July 2018.

[83] American Cancer Society. Cancer facts & figures 2018. Atlanta, GA: American Cancer Society; 2018.

[84] Goverse G, Molenaar R, Macia L, Tan J, Erkelens MN, Konijn T, Mebius RE. Diet-derived short chain fatty acids stimulate intestinal epithelial cells to induce mucosal tolerogenic dendritic cells. J Immunol 2017;198(5):2172–81. https://doi.org/10.4049/jimmunol.1600165.

[85] Wong J, de Souza R, Kendall C, Emam A, Jenkins D. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006;40(3):235–43.

[86] Le Poul EL, Loison C, Struyf S, Springael J, Lannoy V, Decobecq M, Detheux M. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. J Biol Chem 2003;278(28):25481–9. https://doi.org/10.1074/jbc.M301403200.

[87] He C, Shi Y, Wu R, Sun M, Fang L, Wu W, Liu Z. miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-alpha in IBD. Gut 2016;65(12):1938. https://doi.org/10.1136/gutjnl-2015-309389.

[88] Fransen F, van Beek AA, Borghuis T, Meijer B, Hugenholtz F, van der Gaast-de Jongh CE, Vos P. The impact of gut microbiota on gender-specific differences in immunity. Front Immunol 2017;8:754. https://doi.org/10.3389/fimmu.2017.00754.

[89] Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 2008;8(9):737–44. https://doi.org/10.1038/nri2394.

[90] vom Steeg LG, Klein SL. SeXX matters in infectious disease pathogenesis. PLoS Pathog 2016;12(2). https://doi.org/10.1371/journal.ppat.1005374.

[91] Tremellen K. Gut endotoxin leading to a decline IN gonadal function (GELDING) - a novel theory for the development of late onset hypogonadism in obese men. Basic Clin Androl 2016;26(1):7. https://doi.org/10.1186/s12610-016-0034-7.

[92] Tremellen K, McPhee N, Pearce K, Benson S, Schedlowski M, Engler H. Endotoxin-initiated inflammation reduces testosterone production in men of reproductive age. Am J Physiol Endocrinol Metab 2018;314(3):E206–13. https://doi.org/10.1152/ajpendo.00279.2017.

[93] Trumble BC, Blackwell AD, Stieglitz J, Thompson ME, Suarez IM, Kaplan H, Gurven M. Associations between male testosterone and immune function in a pathogenically stressed forager-horticultural population. Am J Phys Anthropol 2016;161(3):494–505. https://doi.org/10.1002/ajpa.23054.

[94] Golombos DM, Ayangbesan A, O'Malley P, Lewicki P, Barlow L, Barbieri CE, Scherr DS. The role of gut microbiome in the pathogenesis of prostate cancer: a prospective, pilot study. Urology 2018;111:122–8. https://doi.org/10.1016/j.urology.2017.08.039.

[95] Porter CM, Shrestha E, Peiffer LB, Sfanos KS. The microbiome in prostate inflammation and prostate cancer. Prostate Cancer Prostatic Dis 2018. https://doi.org/10.1038/s41391-018-0041-1.

[96] Liss MA, White JR, Goros M, Gelfond J, Leach R, Johnson-Pais T, Shah DP. Metabolic biosynthesis pathways identified from fecal microbiome associated with prostate cancer. Eur Urol 2018. https://doi.org/10.1016/j.eururo.2018.06.033.

[97] Slocum C, Kramer C, Genco CA. Immune dysregulation mediated by the oral microbiome: potential link to chronic inflammation and atherosclerosis. J Intern Med 2016;280(1):114–28. https://doi.org/10.1111/joim.12476.

[98] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Hazen SL. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472(7341):57–63. https://doi.org/10.1038/nature09922.

[98a] Koeth R, Levison B, Culley M, Buffa J, Wang Z, Gregory J, et al. gamma-Butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. Cell Metab 2014;20(5):799–812. https://doi.org/10.1016/j.cmet.2014.10.006.

[99] Komaroff AL. The microbiome and risk for atherosclerosis. JAMA 2018;319(23):2381. https://doi.org/10.1001/jama.2018.5240.

[100] Spence JD. Intestinal microbiome and atherosclerosis. EBioMedicine 2016;13:17–8. https://doi.org/10.1016/j.ebiom.2016.10.033.

[101] Bogiatzi C, Gloor G, Allen-Vercoe E, Reid G, Wong RG, Urquhart BL, Spence JD. Metabolic products of the intestinal microbiome and extremes of atherosclerosis. Atherosclerosis 2018;273:91–7. https://doi.org/10.1016/j.atherosclerosis.2018.04.015.

[102] Kasselman LJ, Vernice NA, DeLeon J, Reiss AB. The gut microbiome and elevated cardiovascular risk in obesity and autoimmunity. Atherosclerosis 2018;271:203–13. https://doi.org/10.1016/j.atherosclerosis.2018.02.036.

[103] Suganami T, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, Mizuarai S, Ogawa Y. Role of the toll-like receptor 4/NF-kappaB pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages. Arterioscler Thromb Vasc Biol 2007;27(1):84.

[104] Williams NT. Probiotics. Am J Health Syst Pharm 2010;67(6):449–58. https://doi.org/10.2146/ajhp090168.

[105] Bell V, Ferrão J, Fernandes T. Nutritional guidelines and fermented food frameworks. Foods 2017;6(8):65. https://doi.org/10.3390/foods6080065.

[106] Zou J, Dong J, Yu X. Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for helicobacter pylori eradication. Helicobacter 2009;14(5):97. https://doi.org/10.1111/j.1523-5378.2009.00716.x.

[107] Chiu H, Chen Y, Lu Y, Han Y, Shen Y, Venkatakrishnan K, Wang C. Regulatory efficacy of fermented plant extract on the intestinal microflora and lipid profile in mildly hypercholesterolemic individuals. J Food Drug Anal 2017;25(4):819–27. https://doi.org/10.1016/j.jfda.2016.10.008.

[108] Wang C, Nagata S, Asahara T, Yuki N, Matsuda K, Tsuji H, Yamashiro Y. Intestinal microbiota profiles of healthy pre-school and school-age children and effects of probiotic supplementation. Ann Nutr Metab 2015;67(4):257–66. https://doi.org/10.1159/000441066.

[109] Veiga P, Pons N, Agrawal A, Oozeer R, Guyonnet D, Brazeilles R, Kennedy SP. Changes of the human gut microbiome induced by a fermented milk product. Sci Rep 2014/2015;4(1):6328. https://doi.org/10.1038/srep06328.

[110] Elli M, Callegari ML, Ferrari S, Bessi E, Cattivelli D, Soldi S, Antoine J-M. Survival of yogurt bacteria in the human gut. Appl Environ Microbiol 2006;72(7):5113–7. https://doi.org/10.1128/AEM.02950-05.

[111] Bezkorovainy A. Probiotics: determinants of survival and growth in the gut. Am J Clin Nutr 2001;73(2):399s–405s. https://doi.org/10.1093/ajcn/73.2.399s.

[112] Osborn DA, Sinn JKH. Probiotic supplements. Br Med J 2013;347. https://doi.org/10.1136/bmj.f7138.

[113] Gomaa EZ. Effect of prebiotic substances on growth, fatty acid profile and probiotic characteristics of Lactobacillus brevis NM101-1. Microbiology 2017;86(5):618–28. https://doi.org/10.1134/S0026261717050095.

[114] Vandenplas Y, Huys G, Daube G. Probiotics: an update. J Pediatr 2015;91(1):6–21. https://doi.org/10.1016/j.jped.2014.08.005.

[115] Quagliariello A, Aloisio I, Cionci NB, Luiselli D, D'Auria G, Martinez-Priego L, Gioia DD. Effect of Bifidobacterium breve on the intestinal microbiota of coeliac children on a gluten free diet: a pilot study. Nutrients 2016;8(10):660. https://doi.org/10.3390/nu8100660.

[116] Klemenak M, Dolinšek J, Langerholc T, Di Gioia D, Mičetić-Turk D. Administration of Bifidobacterium breve decreases the production of TNF-α in children with celiac disease. Dig Dis Sci 2015;60(11):3386–92. https://doi.org/10.1007/s10620-015-3769-7.

[117] Klarin B, Wullt M, Palmquist I, Molin G, Larsson A, Jeppson B, Institutionen för kirurgiska vetenskaper. Lactobacillus plantarum 299v reduces colonisation of clostridium difficile in critically ill patients treated with antibiotics. Acta Anaesthesiol Scand 2008;52(8):1096–102. https://doi.org/10.1111/j.1399-6576.2008.01748.x.

[118] Castagliuolo I, Riegler MF, Valenick L, LaMont JT, Pothoulakis C. Saccharomyces boulardii protease inhibits the effects of Clostridium difficile toxins A and B in human colonic mucosa. Infect Immun 1999;67(1):302–7.

[119] Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Esmaillzadeh A. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition 2016;32(3):315–20. https://doi.org/10.1016/j.nut.2015.09.003.

[120] Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. Brain Behav Immun 2015;48:258–64. https://doi.org/10.1016/j.bbi.2015.04.003.

[121] Pirbaglou M, Katz J, de Souza RJ, Stearns JC, Motamed M, Ritvo P. Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials. Nutr Res 2016;36(9):889–98. https://doi.org/10.1016/j.nutres.2016.06.009.

[122] Gerasimov SV, Vasjuta VV, Myhovych OO, Bondarchuk LI. Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial.

Am J Clin Dermatol 2010;11(5):351–61. https://doi.org/10.2165/11531420-000000000-00000.

[123] Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003;361(9372):1869–71. https://doi.org/10.1016/S0140-6736(03)13490-3.

[124] Isolauri E, Arvola T, Sütas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;30(11):1604.

[125] Doron S, Gorbach SL. Probiotics: their role in the treatment and prevention of disease. Expert Rev Anti-Infect Ther 2006;4(2):261–75. https://doi.org/10.1586/14787210.4.2.261.

[126] Liu Z, Shen T, Zhang P, Ma Y, Qin H. Lactobacillus plantarum surface layer adhesive protein protects intestinal epithelial cells against tight junction injury induced by enteropathogenic Escherichia coli. Mol Biol Rep 2010;38(5):3471–80. https://doi.org/10.1007/s11033-010-0457-8.

[127] Asemi Z, Zare Z, Shakeri H, Sabihi S, Esmaillzadeh A. Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. Ann Nutr Metab 2013;63(1–2):1–9. https://doi.org/10.1159/000349922.

[128] Collado MC, González R, González A, Hernández M, Ferrús MA, Sanz Y. Antimicrobial peptides are among the antagonistic metabolites produced by bifidobacterium against helicobacter pylori. Int J Antimicrob Agents 2005;25(5):385–91. https://doi.org/10.1016/j.ijantimicag.2005.01.017.

[129] Guslandi M, Mezzi G, Sorghi M, Testoni PA. Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci 2000;45(7):1462.

[130] Guslandi M, Giollo P, Testoni P. A pilot trial of Saccharomyces boulardii in ulcerative colitis. Eur J Gastroenterol Hepatol 2003;15:697–8. https://doi.org/10.1097/01.meg.0000059138.68845.06.

[130a] Haller D, Antoine J, Bengmark S, Enck P, Rijkers G, Lenoir-Wijnkoop I, Haller D. Guidance for substantiating the evidence for beneficial effects of probiotics: probiotics in chronic inflammatory bowel disease and the functional disorder irritable bowel syndrome. J Nutr 2010;140(3):690S–6907S. https://doi.org/10.3945/jn.109.113746.

[131] Mohammad M, Hussein L, Yamamah G, Rawi S. The impact of probiotic and or honey supplements on gut permeability among egyptian children. J Nutr Environ Med 2007;16(1):10–5. https://doi.org/10.1080/13590840601016387.

[132] Shing CM, Peake JM, Lim CL, Briskey D, Walsh NP, Fortes MB, Vitetta L. Effects of probiotics supplementation on gastrointestinal permeability, inflammation and exercise performance in the heat. Eur J Appl Physiol 2014;114(1):93–103. https://doi.org/10.1007/s00421-013-2748-y.

[133] Guandalini S, Pensabene L, Zikri M, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 2000;30:54–60.

[134] Van Niel C, Feudtner C, Garrison M, Christakis D. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics 2002;109:678–84.

[135] Lyseng-Williamson K. Bifidobacterium infantis 35624 as a probiotic dietary supplement: a profile of its use. Drugs Ther Perspect 2017;33(8):368–74. https://doi.org/10.1007/s40267-017-04239.

[136] Björklund M, Ouwehand AC, Forssten SD, Nikkilä J, Tiihonen K, Rautonen N, Lahtinen SJ. Gut microbiota of healthy elderly NSAID users is selectively modified with the administration of Lactobacillus acidophilus NCFM and lactitol. Age 2012;34(4):987–99. https://doi.org/10.1007/s11357-011-9294-5.

[137] Andreasen AS, Larsen N, Pedersen-Skovsgaard T, Berg RMG, Møller K, Svendsen KD, Pedersen BK. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr 2010;104(12):1831–8. https://doi.org/10.1017/S0007114510002874.

[138] Hojsak I, Abdovi'c S, Szajewska H, Milosevi'c M, Krznari'c Z, Kolacek S. Lactobacillus G.G. in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 2010;125:e1171–7.18.

[139] Zhang H, Zhang L, Yeh C, Jin Z, Ding L, Liu BY, Dannelly HK. Prospective study of probiotic supplementation results in immune stimulation and improvement of upper respiratory infection rate. Synth Syst Biotechnol 2018;3(2):113–20. https://doi.org/10.1016/j.synbio.2018.03.001.

[140] Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, Sharif S, Asghari-Jafarabadi M, Zavvari S. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. Nutrition 2014;30(4):430–5. https://doi.org/10.1016/j.nut.2013.09.007.

[141] Zamani B, Golkar HR, Farshbaf S, Emadi-Baygi M, Tajabadi-Ebrahimi M, Jafari P, Asemi Z. Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Int J Rheum Dis 2016;19(9):869–79. https://doi.org/10.1111/1756-185X.12888.

[142] Ozdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. Clin Exp Immunol 2010;160(3):295–304. https://doi.org/10.1111/j.1365-2249.2010.04109.x.

[143] Palócz O, Pászti-Gere E, Gálfi P, Farkas O. Chlorogenic acid combined with lactobacillus plantarum 2142 reduced LPS-induced intestinal inflammation and oxidative stress in IPEC-J2 cells. PLoS ONE 2016;11(11). https://doi.org/10.1371/journal.pone.0166642.

[144] Caillard R, Lapointe N. In vitro gastric survival of commercially available probiotic strains and oral dosage forms. Int J Pharm 2017;519(1–2):125–7. https://doi.org/10.1016/j.ijpharm.2017.01.019.

[145] Ellis ML, Shaw KJ, Jackson SB, Daniel SL, Knight J. Analysis of commercial kidney stone probiotic supplements. Urology 2015;85(3):517–21. https://doi.org/10.1016/j.urology.2014.11.013.

[146] Katz J, Pirovano F, Matteuzzi D, et al. Commercially available probiotic preparations: are you getting what you pay for? Gastroenterology 2002;122(Suppl. 1):A-459. Abstract.

[147] Cutting S, Fraser P, Payne K. Probiotic potential spore-forming bacteria. Nutraceutical Bus Technol 2008;4(5):5.

[148] Lakshmi SG, Jayanthi N, Saravanan M, Ratna MS. Safety assessment of Bacillus clausii UBBC07, a spore forming probiotic. Toxicol Rep 2017;4:62–71. https://doi.org/10.1016/j.toxrep.2016.12.004.

[149] Elshaghabee FMF, Rokana N, Gulhane RD, Sharma C, Panwar H. Bacillus as potential probiotics: status, concerns, and future perspectives. Front Microbiol 2017;8:1490. https://doi.org/10.3389/fmicb.2017.01490.

[150] Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter bacteroidetes and firmicutes in lean and obese JCR: LA-cp rats. Br J Nutr 2012;107(4):601–13. https://doi.org/10.1017/S0007114511003163.

[151] Caetano BFR, de Moura NA, Almeida APS, Dias MC, Sivieri K, Barbisan LF. Yacon (Smallanthus sonchifolius) as a food supplement: health-promoting benefits of fructooligosaccharides. Nutrients 2016;8(7):436. https://doi.org/10.3390/nu8070436.

[152] Shi Y, Zhai Q, Li D, Mao B, Liu X, Zhao J, Chen W. Restoration of cefixime-induced gut microbiota changes by lactobacillus cocktails and fructooligosaccharides in a mouse model. Microbiol Res 2017;200:14–24. https://doi.org/10.1016/j.micres.2017.04.001.

[153] Davis LMG, Martínez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. PLoS ONE 2011;6(9). https://doi.org/10.1371/journal.pone.0025200.

[154] Azcarate-Peril MA, Ritter AJ, Savaiano D, Monteagudo-Mera A, Anderson C, Magness ST, Klaenhammer TR. Impact of short-chain galactooligosaccharides on the gut microbiome of lactose-intolerant individuals. Proc Natl Acad Sci U S A 2017;114(3):E367–75.

[155] So D, Whelan K, Rossi M, Morrison M, Holtmann G, Kelly JT, Campbell KL. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. Am J Clin Nutr 2018;107(6):965–83. https://doi.org/10.1093/ajcn/nqy041.

[156] Carlson JL, Erickson JM, Hess JM, Gould TJ, Slavin JL. Prebiotic dietary fiber and gut health: Comparing the in vitro fermentations of beta-glucan, inulin and xylooligosaccharide. Nutrients 2017;9(12):1361. https://doi.org/10.3390/nu9121361.

[157] Christensen EG, Licht TR, Leser TD, Bahl MI. Dietary xylo-oligosaccharide stimulates intestinal bifidobacteria and lactobacilli but has limited effect on intestinal integrity in rats. BMC Res Notes 2014;7:660. https://doi.org/10.1186/1756-0500-7-660.

[158] Nieto-Domínguez M, de Eugenio LI, York-Durán MJ, Rodríguez-Colinas B, Plou FJ, Chenoll E, … Jesús Martínez M. Prebiotic effect of xylooligosaccharides produced from birchwood xylan by a novel fungal GH11 xylanase. Food Chem 2017;232:105–13. https://doi.org/10.1016/j.foodchem.2017.03.149.

[159] Van den Abbeele P, Duysburgh C, Jiang TA, Rebaza M, Pinheiro I, Marzorati M. A combination of xylooligosaccharides and a polyphenol blend affect microbial composition and activity in the distal colon exerting immunomodulating properties on human cells. J Funct Foods 2018;47:163–71. https://doi.org/10.1016/j.jff.2018.05.053.

[160] Alfa MJ, Strang D, Tappia PS, Graham M, Van Domselaar G, Forbes JD, Lix LM. A randomized trial to determine the impact of a digestion resistant starch composition on the gut microbiome in older and mid-age adults. Clin Nutr 2017/2018;37(3):797–807. https://doi.org/10.1016/j.clnu.2017.03.025.

[161] Hald S, Schioldan AG, Moore ME, Dige A, Helle NL, Agnholt J, Dahlerup JF. Effects of arabinoxylan and resistant starch on intestinal microbiota and short-chain fatty acids in subjects with metabolic syndrome: a randomised crossover study. PLoS ONE 2016;11(7). https://doi.org/10.1371/journal.pone.0159223.

[162] Maier TV, Lucio M, Lee LH, VerBerkmoes NC, Brislawn CJ, Bernhardt J, Jansson JK. Impact of dietary resistant starch on the human gut microbiome, metaproteome, and metabolome. MBio 2017;8(5). https://doi.org/10.1128/mBio.01343-17.

[163] Venkataraman A, Sieber JR, Schmidt AW, Waldron C, Theis KR, Schmidt TM. Variable responses of human microbiomes to dietary supplementation with resistant starch. Microbiome 2016;4(1):33. https://doi.org/10.1186/s40168-016-0178-x.

[164] Fukunaga T, Sasaki M, Araki Y, Okamoto T, al, e. Effects of the soluble fibre pectin on intestinal cell proliferation, fecal short chain fatty acid production and microbial population. Digestion 2003;67(1):42–9. Retrieved from, https://search-proquest-com.ezproxy2.apus.edu/docview/195194733?accountid=8289.

[165] Bouhnik Y, Alain S, Attar A, Flourié B, Raskine L, Sanson-Le Pors MJ, Rambaud JC. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999;94(5):1327–31.

[166] Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol 2007;3(2):112–22.

[167] Husebye E. The pathogenesis of gastrointestinal bacterial overgrowth. Chemotherapy 2005;51(1):1–22. https://doi.org/10.1159/000081988.

[168] Lewis SJ, Franco S, Young G, O'Keefe SJ. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. Aliment Pharmacol Ther 1996;10:557–61. https://doi.org/10.1046/j.1365-2036.1996.d01-506.x.

[169] Saltzman JR, Russell R. Nutritional consequences of intestinal bacterial overgrowth. Compr Ther 1994;20(9):523–30.

[170] Crinnion WJ. Organic foods contain higher levels of certain nutrients, lower levels of pesticides, and may provide health benefits for the consumer. Altern Med Rev 2010;15(1):4.

[171] Barbieri R, Coppo E, Marchese A, Daglia M, Sobarzo-Sánchez E, Nabavi SF, Nabavi SM. Phytochemicals for human disease: an update on plant-derived compounds antibacterial activity. Microbiol Res 2017;196:44–68. https://doi.org/10.1016/j.micres.2016.12.003.

[172] He Y, Yuan X, Zhou G, Feng A. Activation of IGF-1/IGFBP-3 signaling by berberine improves intestinal mucosal barrier of rats with acute endotoxemia. Fitoterapia 2018;124:200–5. https://doi.org/10.1016/j.fitote.2017.11.012.

[173] Stermitz FR, Lorenz P, Tawara JN, Zenewicz LA, Lewis K. Synergy in a medicinal plant: antimicrobial action of berberine potentiated by 5′-methoxyhydnocarpin, a multidrug pump inhibitor. Proc Natl Acad Sci U S A 2000;97(4):1433–7. https://doi.org/10.1073/pnas.030540597.

[174] Catinean A, Neag MA, Muntean DM, Bocsan IC, Buzoianu AD. An overview on the interplay between nutraceuticals and gut microbiota. Peerj 2018;6. https://doi.org/10.7717/peerj.4465.

[175] Altintas A, Tabanca N, Tyihák E, Ott PG, Móricz AM, Mincsovics E, Wedge DE. Characterization of volatile constituents from origanum onites and their antifungal and antibacterial activity. J AOAC Int 2013;96(6):1200–8. https://doi.org/10.5740/jaoacint.SGEAltintas.

[176] Fournomiti M, Kimbaris A, Mantzourani I, Plessas S, Theodoridou I, Papaemmanouil V, Alexopoulos A. Antimicrobial activity of essential oils of cultivated oregano (Origanum vulgare), sage (Salvia officinalis), and thyme (Thymus vulgaris) against clinical isolates of Escherichia coli, Klebsiella oxytoca, and Klebsiella pneumoniae. Microb Ecol Health Dis 2015;26:1–7. https://doi.org/10.3402/mehd.v26.23289.

[177] Baskaran SA, Kollanoor-Johny A, Nair MS, Venkitanarayanan K. Efficacy of plant-derived antimicrobials in controlling enterohemorrhagic Escherichia coli virulence in vitro. J Food Protect 2016;79(11):1965–70. https://doi.org/10.4315/0362-028X.JFP-16-104.

[178] Nabavi SF, Nabavi SM, Marchese A, Izadi M, Curti V, Daglia M. Plants belonging to the genus thymus as antibacterial agents: From farm to pharmacy. Food Chem 2015;173:339–47. https://doi.org/10.1016/j.foodchem.2014.10.042.

[179] Utchariyakiat I, Surassmo S, Jaturanpinyo M, Khuntayaporn P, Mullika TC. Efficacy of cinnamon bark oil and cinnamaldehyde on anti-multidrug resistant pseudomonas aeruginosa and the synergistic effects in combination with other antimicrobial agents. BMC Complement Altern Med 2016;16. https://doi.org/10.1186/s12906-016-1134-9.

[180] Zhang X, Jiang A, Qi B, Ma Z, Xiong Y, Dou J, Wang J. Resveratrol protects against helicobacter pylori-associated gastritis by combating oxidative stress. Int J Mol Sci 2015;16(11):27757–69. https://doi.org/10.3390/ijms161126061.

[181] Queipo-Ortuño M, Boto-Ordóñez M, Murri M, Gomez-Zumaquero J, Clemente-Postigo M, Estruch R, Cardona Diaz F, Andrés-Lacueva C, Tinahones F. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. Am J Clin Nutr 2012;95(6):1323–34. https://doi.org/10.3945/ajcn.111.027847.

[182] Kaulmann A, Bohn T. Bioactivity of polyphenols: Preventive and adjuvant strategies toward reducing inflammatory bowel diseases-promises, perspectives, and pitfalls. Oxid Med Cell Longev 2016. https://doi.org/10.1155/2016/9346470.

[183] Bereswill S, Muñoz M, Fischer A, Plickert R, Haag L, Otto B, Heimesaat MM. Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation. PLoS ONE 2010;5(12). https://doi.org/10.1371/journal.pone.0015099.

[184] Ohno M, Nishida A, Sugitani Y, Nishino K, Inatomi O, Sugimoto M, Andoh A. Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. PLoS ONE 2017;12(10). https://doi.org/10.1371/journal.pone.0185999.

[185] Shen L, Liu L, Ji H. Regulative effects of curcumin spice administration on gut microbiota and its pharmacological implications. Food Nutr Res 2017;61:1–4. https://doi.org/10.1080/16546628.2017.1361780.

[186] Hassaninasab A, Hashimoto Y, Tomita-Yokotani K, Kobayashi M. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. Proc Natl Acad Sci U S A 2011;108(16):6615–20. https://doi.org/10.1073/pnas.1016217108.

[187] Duda-Chodak A, Tarko T, Satora P, Sroka P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. Eur J Nutr 2015;54(3):325–41. https://doi.org/10.1007/s00394-015-0852-y.

[188] Vaquero MJR, Alberto MR, de Nadra MCM. Antibacterial effect of phenolic compounds from different wines. Food Control 2007;18(2):93–101. https://doi.org/10.1016/j.foodcont.2005.08.010.

[189] Williamson G, Clifford MN. Colonic metabolites of berry polyphenols: the missing link to biological activity? Br J Nutr 2010;104:S48–66. https://doi.org/10.1017/S0007114510003946.

[190] Kahle K, Kraus M, Scheppach W, Ackermann M, Ridder F, Richling E. Studies on apple and blueberry fruit constituents: do the polyphenols reach the colon after ingestion? Mol Nutr Food Res 2006;50:418–23. https://doi.org/10.1002/mnfr.200500211.

[191] Sato Y, Itagaki S, Kurokawa T, Ogura J, Kobayashi M, Hirano T, Iseki K. In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. Int J Pharm 2011;403(1–2):136–8. https://doi.org/10.1016/j.ijpharm.2010.09.035.

[192] Jamar G, Estadella D, Pisani LP. Contribution of anthocyanin-rich foods in obesity control through gut microbiota interactions. Biofactors 2017;43(4):507–16. https://doi.org/10.1002/biof.1365.

[193] Zhang P, Zhang M, He S, Cao X, Sun H, Chen X, Ye Y. Extraction and probiotic properties of new anthocyanins from purple sweet potato (Solanum tuberosum), Curr Top Nutraceutical Res 2016;14(2):153–60. Retrieved from, https://search-proquest-com.ezproxy1.apus.edu/docview/1870902562?accountid=8289.

[194] Sahib N, Anwar F, Gilani A, Hamid A, Saari N, Alkharfy K. Coriander (Coriandrum sativum L.): a potential source of high-value components for functional foods and nutraceuticals – a review. Phytother Res 2013;(10):1439.

[195] Xiao S, Li Q, Hu K, He Y, Ai Q, Hu L, Yu J. Vitamin A and retinoic acid exhibit protective effects on necrotizing enterocolitis by regulating intestinal flora and enhancing the intestinal epithelial barrier. Arch Med Res 2018. https://doi.org/10.1016/j.arcmed.2018.04.003.

[196] Holder BS, Grant CR, Liberal R, Ma Y, Heneghan MA, Mieli-Vergani G, Longhi MS. Retinoic acid stabilizes antigen-specific regulatory T-cell function in autoimmune hepatitis type 2. J Autoimmun 2014;53:26–32. https://doi.org/10.1016/j.jaut.2014.02.001.

[197] Clark A, Mach N. Role of vitamin D in the hygiene hypothesis: the interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. Front Immunol 2016;7:627.

[198] Biesalski HK. Nutrition meets the microbiome: micronutrients and the microbiota. Ann N Y Acad Sci 2016;1372(1):53–64. https://doi.org/10.1111/nyas.13145.

[199] Mielcarz DW, Kasper LH. The gut microbiome in multiple sclerosis. Curr Treat Options Neurol 2015;17. https://doi.org/10.1007/s11940-015-0344-7.

[200] Ghaly S, Kaakoush NO, Lloyd F, McGonigle T, Mok D, Baird A, Hart PH. High dose vitamin D supplementation alters faecal microbiome and predisposes mice to more severe colitis. Sci Rep 2018;8:1–12. https://doi.org/10.1038/s41598-018-29759-y.

[201] Gominak SC. Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a "pro-inflammatory" state associated with atherosclerosis and autoimmunity. Med Hypotheses 2016;94:103.

[202] Bashir M, Prietl B, Tauschmann M, Mautner SI, Kump PK, Treiber G, Pieber TR. Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. Eur J Nutr 2016;55(4):1479–89. https://doi.org/10.1007/s00394-015-0966-2.

[203] Xiao G, Tang L, Yuan F, Zhu W, Zhang S, Liu Z, Su L. Eicosapentaenoic acid enhances heat stress-impaired intestinal epithelial barrier function in caco-2 cells. PLoS ONE 2013;8(9) https://doi.org/10.1371/journal.pone.0073571.

[204] Menni C, Zierer J, Pallister T, Jackson MA, Long T, Mohney RP, Valdes AM. Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women. Sci Rep 2017;7(1):1. https://doi.org/10.1038/s41598-017-10382-2.

[205] Mokkala K, Laitinen K, Röytiö H. Bifidobacterium lactis 420 and fish oil enhance intestinal epithelial integrity in caco-2 cells. Nutr Res 2016;36(3):246–52. https://doi.org/10.1016/j.nutres.2015.11.014.

[206] Costantini L, Molinari R, Farinon B, Merendino N. Impact of omega-3 fatty acids on the gut microbiota. Int J Mol Sci 2017;18(12):2645. https://doi.org/10.3390/ijms18122645.

[207] Liu T, Hougen H, Vollmer AC, Hiebert SM. Gut bacteria profiles of Mus musculus at the phylum and family levels are influenced by saturation of dietary fatty acids. Anaerobe 2012;18(3):331–7. https://doi.org/10.1016/j.anaerobe.2012.02.004.

[208] Yu H, Zhu J, Pan W, Shen S, Shan W, Das UN. Effects of fish oil with a high content of n-3 polyunsaturated fatty acids on mouse gut microbiota. Arch Med Res 2014;45(3):195–202. https://doi.org/10.1016/j.arcmed.2014.03.008.

[209] Balfego M, Canivell S, Hanzu FA, Sala-Vila A, Martinez-Medina M, Murillo S, Aranda G. Effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naive patients with type 2 diabetes: a pilot randomized trial. Lipids Health Dis 2016;15. https://doi.org/10.1186/s12944-016-0245-0.

[210] Beutheu S, Ghouzali I, Galas L, Déchelotte P, Coëffier M. Glutamine and arginine improve permeability and tight junction protein expression in methotrexate-treated caco-2 cells. Clin Nutr 2013;32(5):863–9. https://doi.org/10.1016/j.clnu.2013.01.014.

[211] de Souza AZ, Zambom AZ, Abboud KY, Reis SK, Tannihão F, Guadagnini D, Prada PO. Oral supplementation with l -glutamine alters gut microbiota of obese and overweight adults: a pilot study. Nutrition 2015;31(6):884–9. https://doi.org/10.1016/j.nut.2015.01.004.

[212] Beutheu S, Ouelaa W, Guérin C, Belmonte L, Aziz M, Tennoune N, Coëffier M. Glutamine supplementation, but not combined glutamine and arginine supplementation, improves gut barrier function during chemotherapy-induced intestinal mucositis in rats. Clin Nutr 2013/2014;33(4):694–701. https://doi.org/10.1016/j.clnu.2013.09.003.

[213] Rao R, Samak G. Role of glutamine in protection of intestinal epithelial tight junctions. J Epithel Biol Pharmacol 2012;5(Suppl 1-M7):47–54. https://doi.org/10.2174/1875044301205010047.

[214] Ren W, Wang K, Yin j, Chen S, Liu G, Tan B, Yin Y. Glutamine on intestinal secretory immunoglobulin A secretion: a mechanistic perspective. Front Immunol 2016;7. https://doi.org/10.3389/fimmu.2016.00503.

Further Reading

[215] Andermann TM, Rezvani A, Bhatt AS. Microbiota manipulation with prebiotics and probiotics in patients undergoing stem cell transplantation. Curr Hematol Malig Rep 2016;11 (1):19–28. https://doi.org/10.1007/s11899-016-0302-9.

[216] Rothwell JA, Pérez-Jiménez J, Neveu V, Medina-Ramon A, M'Hiri N, Garcia Lobato P, Manach C, Knox K, Eisner R, Wishart D, Scalbert A. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database 2013. https://doi.org/10.1093/database/bat070. [Accessed 2 August 2018].