

Modulation of gut-microbiota through probiotics and dietary interventions to improve host health

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Abstract

Dietary patterns play an important role in regards to the modulation and control of the gut microbiome composition and function. The interaction between diet and microbiota plays an important role in order to maintain intestinal homeostasis, which ultimately affect the host's health. Diet directly impacts the microbes that inhabit the gastrointestinal tract (GIT), which then contributes to the production of secondary metabolites, such as short-chain fatty acids, neurotransmitters, and antimicrobial peptides. Dietary consumption with genetically modified probiotics can be the best vaccine delivery vector and protect cells from various illnesses. A holistic approach to disease prevention, treatment, and management takes these intrinsically linked diet-microbes, microbe-microbe interactions, and microbe-host interactions into account. Dietary components, such as fiber can modulate beneficial gut microbiota, and they have resulting ameliorative effects against metabolic disorders. Medical

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interventions, such as antibiotic drugs can conversely have detrimental effects on gut microbiota by disputing the balance between *Bacteroides* and *Firmicute*, which contribute to continuing disease states. We summarize the known effects of various dietary components, such as fibers, carbohydrates, fatty acids, vitamins, minerals, proteins, phenolic acids, and antibiotics on the composition of the gut microbiota in this article in addition to the beneficial effect of genetically modified probiotics and consequently their role in regards to shaping human health.

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INTRODUCTION

The human body is divided into multiple microhabitats, which all host complex microbial communities that are key to an individual's overall health. Disturbance of the usually balanced metabolic state of these microhabitats can have dire consequences on the overall health and the disease susceptibility of the host if not appropriately counterbalanced.¹ The gastrointestinal tract (GIT) and its microbial inhabitants have long been recognized as maintaining the host's health, and they are a valuable key indicator of the host's metabolic status. Diet and other orally administered compounds have been known to directly affect the microbiome composition and function in the GIT system,² but it is now widely accepted that the microbiome composition and function can also be altered via less direct means, such as regular diet, physical activity, or stress.³

Complex microbial communities related to health and disease exist in the human gut. Several environmental influences, such as particular diets, continuously alter the gut microbiome.⁴ Few microbial phyla dominate the human gut microbiota, which includes *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Verrucomicrobia*. Other phyla, such as *Cyanobacteria*, *Fusobacteria*, *Lentisphaerae*, *Spirochaetes*, and TM7 are also present. These resident microorganisms are essential for the proper function of the gut ecosystem and aid in host metabolism even when present in a small fraction by converting ingested complex carbohydrates to simple sugars. The ingestion of a fiber-rich diet results in a downstream metabolic profile that includes lactate, succinate, and short-chain fatty acids (SCFAs), such as acetate, butyrate, and propionate,⁵ and the resulting metabolites are significant contributors to the growth and cellular function of gut microbes.⁶ Replacing a fiber-rich diet with high fat alters metabolic end products, which leads to shifting metabolic profiles and potential disease onset.⁷

Infections are a common threat to the host's health, and there is a regulated system that is aimed at ridding the body of pathogens.⁸ The tight regulation of the gut environment and its associated microbiome is specifically the crucial barrier that aids in preventing and mitigating infections and close synergistic relationships between the gut, gut microbiome, and the host's immune system.⁹ Antibiotic treatment, high-fat diets, stress, and disease disturb the fine interactions and gut homeostasis.¹ This disturbance leads to shifting metabolic profiles that alter the gut microbiota, which results in an altered feedback loop that can impair the host's health.¹⁰ For example, bacteria, such as *Collinsella aerofaciens* DSM 3979, *Eubacterium rectale* A1-86, and *Prevotella copri* DSM 18205 produce hydrogen during fermentation,¹¹ which inhibits the metabolic activity of many benign gut microbes but increases the activity of the hydrogen sulfate-reducing bacterium *Desulfovibrio piger*.¹² The gut microbiome can be altered by administering a healthy diet and probiotics.

The Greek word *probiotic* implies *favor*, and the Greek word *biotic* implies *life*. Probiotics are living microorganisms that have beneficial effects on the host in significant parts via regulating the intestinal microbiota.¹³ Both humans and animals can benefit from the therapeutic use of probiotics for prevention and treatment. Humans have been consuming beneficial microorganisms for food, nutrition, and health for centuries, but the precise number of probiotic bacteria that is needed in order to provide positive health effects can vary from strain to strain. The lowest level that is considered sufficient is 10⁶ live bacteria per gram or milliliter of the food product.¹⁴ Probiotics provide a wide range of potential advantages, which include metabolic regulation, preventing opportunistic pathogens from colonizing the intestine, lowering lactose intolerance, and maintaining a healthy gut flora balance.¹⁵ Lactic acid bacilli contrarily cause diseases, such as endocarditis, bacteremia, and others in vulnerable people as well as the rotting of processed meats, which causes significant financial losses for the food-producing industries.¹⁶ Some enterococci were discovered to have antibiotic-resistant determinants as well as virulence factors, such as adhesins, invasins, and hemolysins.¹⁷

Skepticism has risen regarding probiotics, which is primarily due to their beneficial effects not being fully understood. Also, their usefulness has not been validated in clinical trials in many cases, so interest in the therapeutic use of probiotic microorganisms has increased over the past decade.¹⁸ As a result, probiotic strains with demonstrated probiotic potential being modified in order to enhance their beneficial properties generated a lot of interest. Probiotic strains can also be genetically modified in order to reverse antimicrobial resistance and undergo other changes that make them safer and more useful for human applications.¹⁹ The gut microbiota is influenced by diet and nutritional state, and various products, which include probiotics, prebiotics, and postbiotics, are now readily available to regulate the gut microbiota. New studies examined the impact of probiotics and nutritional supplements in both animal models and human studies with positive outcomes.²⁰ In addition, this study also provided information about diet patterns and their effect on the gut microbiome and the host's health.

DIETARY TYPE

Diet plays an essential role in regard to human health. The consumption of an imbalance, which is an unhealthy diet, has been linked to increased inflammatory responses, oxidative stress, and disease conditions, whereas long-term and consistent consumption of a balanced diet, diet in contrast, had a positive overall health effect.²¹ Industrialization, environmental factors, and their different facets have been linked to increasing autoimmune disorders and metabolic syndrome, which is in line with society-wide awareness about dietary changes. Industrialization has led

to an increase in sedentary lifestyles and decreased exposure to environmental microorganisms that would typically increase the ability of our immune system to respond adequately to pathogens.^{22,23} Distinct differences in the microbial population and metabolic function were observed when the gut microbiomes of a westernized cohort were compared with the gut microbiomes from less industrialized cohorts, indicating that social and cultural factors influence the gut microbiome.²⁴ There is a strong link between gut microbiota and disease conditions, so changes in microbial populations that are caused by voluntary or involuntary lifestyles are significant. For example, an increased Gram-negative bacterial population produces the associated metabolite, lipopolysaccharide (endotoxin), which causes systemic inflammatory disease.²⁵ The therapeutic practice may soon include adjuvant therapies that aim to modify the gut microbiota via dietary modifications due to the strong correlation between the host's health and the gut microbiota composition.²⁶ Dietary changes can also be beneficial,²⁷ successfully demonstrating the altered disease outcome by changing the dietary fiber composition. This suggests that specific dietary choices by individuals can improve intestinal health and reduce metabolic illness.

Vegetarian diet

Cultural beliefs and religious adherence prompted many early human populations to favor plant-based or vegetarian diets,²⁸ and it has been estimated that more than 40% of Americans are shifting toward plant-based diets.²⁹ Plant-based diets with high levels of antioxidants, fiber, and vitamins possess reduced levels of cancer-causing factors, whereas diets with red and processed meats showed links to increased carcinogens.³⁰ Adherence to a vegetarian diet for 3 months led to a modulation of gut microbiota, which reduced metabolic syndrome.³¹ Furthermore, it has been shown that vegetarian diets that are low in fat, such as diets that are commonly found in many regions of India, can have a positive effect against viral infections, which might be potentially due to the protective effects of high antioxidants, minerals, and vitamins in conjunction with the lack of fat.³² The effects of vegetarian diets can counteract oxidative and inflammatory stress, which reduces the risk of aging-related neurological disorders, such as Alzheimer's, Parkinson's, and age-associated cardiovascular disease (CVD).³³

Mediterranean diet

Interest in the Mediterranean diet, which is a diet that is typically rich in vegetables, fruits, whole grains, beans, nuts, seeds, and olive oil, began in the 1960s with the observation that coronary heart disease caused fewer deaths in Mediterranean countries.³⁴ It is well understood that there is a complex relationship between nutrition and immune function,³⁵ and strong immune function is maintained via consuming diets that contain adequate amounts of minerals and vitamins, ultimately reducing the risk of disease. On the contrary, the inadequate consumption of just one vitamin or mineral can impair immunity and threaten illness.³⁵ Dietary intake, the gut microbiome, and the immune system are all interconnected and boost the host's health. The Mediterranean diet supports the growth of beneficial gut bacteria, such as *Bifidobacterium*, *Lactobacilli*, and *Prevotella*, while reducing clostridium-like pathogens. This particular diet type has been linked to improvement in disease conditions, such as lipidaemia, obesity, cancer, inflammation, and diabetes.^{36,37} The high fiber component of the Mediterranean diet, in addition to the lower fat content, may stimulate intestinal microbiota modulation in a way that

the production of beneficial SCFAs, which include butyrate, propionate, and acetate, is increased, and the inflammatory and immune function pathway is regulated.^{38,39}

Japanese diet

The traditional Japanese diet has long been considered to enhance longevity and is considered one of the healthiest diets worldwide. It is characterized by low calories and low cholesterol levels,⁴⁰ which was found to improve the gut microbiome. Green tea, central to the traditional Japanese diet, is high in polyphenols and antioxidants. Fucoxanthin, which is a carotenoid that is found in high concentrations in eatable brown seaweed species, has been shown to possess cancer-mitigating activity⁴¹ as well as inhibit the significant pro-inflammatory cytokines, such as interleukin-1 beta (IL-1 β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF- α). Another typical component of the Japanese diet is fishes, such as tuna and salmon, which are rich in omega-3 fatty acids and protein, and they play a crucial role in breast and colon cancer mitigation.^{42,43} Omega 3 fatty acids and protein-rich sources reduce prostate cancer by suppressing the PI3K/AKT/BAD survival pathway, which induces cell apoptosis, inhibits cell proliferation, and reduces oxidative stress.⁴⁴ Tofu, which is made of soybeans, serves as a common non-meat protein source, and it might convey protection against cancer and oxidative stress via saponin and isoflavones that are found with increased soybean levels.^{45,46}

Ketogenic diets

Ketogenic diets have become popular in recent years, and they are low in carbohydrates and high in fat and proteins. Ketogenic diets modulate gut microbiota by increasing the abundance of beneficial bacteria, such as *Odoribacter* and *Lachnospira*, and SCFAs producers, such as *Muciniphila*, *Lactobacillus*, and *Akkermansia*.⁴⁷ A low-calorie and protein-rich diet can reduce tumor growth and inflammation that is associated with gut dysbiosis and negative health states,⁴⁸ which is in addition to being suggested as a treatment against cancer, obesity, and other metabolic disorders. In addition, there seems to be evidence that it might reduce the risk of disorders related to the central nervous system.⁴⁹

DIET AND INTESTINAL INTEGRITY

A balanced diet provides essential nutrients, which aids in maintaining the symbiotic relationship between the host and gut microbiota. A balanced diet is characterized by adequate calories, vitamins, proteins, and minerals in order to meet homeostatic needs. Adequate nutrition shields the intestines via mucus production by activating goblet cells and Paneth cells, which can produce antimicrobial defensins, such as α -defensins,⁵⁰ and further protection against pathogenic invasion.⁵¹ Combining a well-developed mucus layer and indigenous antimicrobial compounds can inhibit colonization by infectious microbes, which maintains the overall gut homeostasis and, ultimately, the host's health. Particular components, such as lycopenes, lutein, flavones, anthocyanidins, and catechins, in addition to the minerals and vitamins of a balanced diet, can aid against pathogenic attacks by boosting innate defenses, such as immunoglobulin A (IgA), antimicrobial peptides, mucus, and fucosylation.⁵² Poor diets can conversely impair the intestinal epithelial cells, which leave the host susceptible to enteric infection.² Targeted microbiota

therapies with natural food sources and nutraceuticals may be used in order to promote organism GIT health.⁵³

DIETARY COMPONENTS

Carbohydrates

Carbohydrates are a key component of a healthy diet, which are classified as monogosaccharide, digosaccharide, or oligosaccharide. These sugars are a direct energy source for the brain and a critical substrate for red blood cells.⁵⁴ The body requires a large amount of carbohydrates for proper function, but the excessive ingestion of carbohydrates may lead to diseases such as diabetes and obesity. The increased intake of simple and refined carbohydrates can disturb the microbiome and disrupt its finely honed balance with the host, but healthy carbohydrate-containing fiber diets work in order to maintain GIT integrity. Fiber stimulates microbial fermentation, stabilizes the microbial environment, and promotes increasing beneficial SCFA production, which improves the gut and the host's health.⁵⁵

The excessive consumption of carbohydrates can weaken innate and adaptive immunity and exacerbate certain medical conditions, such as hyperglycemia, even though it is a key component of a balanced diet. Microbial disturbances result in the alteration of the immune function, and they can decrease immunity via phagocytosis reduction, neutrophil migration, and superoxide production, which ultimately compromise immunity that facilitates bacterial and fungal infections.²

Carbohydrates are necessary for basic host functions, but particular carbohydrates remain undigestible. For example, trehalose, also known as mycose, is a disaccharide consisting of an alpha-link, formed by the α, α -1,1-glucoside bond between two glucose molecules. Trehalose is used in the food industry in order to improve the appearance and texture of food, but this indigestible sugar can disrupt intestinal homeostasis. The indigestibility of trehalose at the early stages of the intestinal tract and also into the large intestine is where pathogenic *Clostridium difficile* can capitalize on this substrate. The selected *Clostridium difficile* can naturally digest trehalose efficiently, which results in a hypervirulent effect that is due to the abundance of trehalose in the large intestine, and it leads to the worsening condition of gut microbiota, such as the increase in pathogenic bacteria compared with beneficial bacteria.⁵⁶

Carbohydrates that go undigested by the host are referred to as microbial-accessible carbohydrates. These carbohydrates have been shown to reduce pathogen loading and the suppression of *Clostridium difficile* infection in the digestive systems of mice via the production of antimicrobial compounds, such as SCFAs.²

Fiber

Fiber, which can be further classified as soluble, insoluble, or resistant starch, is a subset of carbohydrates, and it is preferentially digested by the microbes of the GIT as opposed to host-derived enzymes. Fiber consumption provides some medical benefits to the host, which are like protective effects against heart disease and diabetes, and it can increase the sense of satiety via the natural bulkiness of fiber, which helps to counter obesity. A specific subset of fiber, short-chain fructo-oligosaccharides, has been shown to possess a prebiotic effect, which can prevent constipation diarrhea and improve the host's digestion.⁵⁷ Dietary fibers have molecular effects by promoting the formation of SCFAs and gut bacteria. Dietary fibers and microbial populations release compounds that can influence gut immunity. Dietary fiber

metabolites have a crucial target in the gastrointestinal immune barrier, and these compounds signal to the immune cells in the intestine.⁵⁸ Dietary fibers affect biological processes and homeostasis through the metabolites produced by microbial fermentation of nutrients, such as SCFAs, in addition to modifying the makeup of the gut microbiota.

Human breast milk contains growth hormones, cytokines, lactoferrin, chemokines, and bioactive factors, improving a newborn's disease resistance and protecting them from enteric infection.⁵⁹ Infants who consume breast milk encounter a particular set of complex carbohydrates that are called human milk oligosaccharides (HMOs). These HMOs act as prebiotics for infant intestinal microbiota, and they provide health benefits and protective effects, such as reduced intestinal pathogenic infections.⁶⁰ Fractionated sections of HMOs have been shown to have anti-adhesive properties against pathogenic bacteria enteropathogenic *Escherichia coli* (EPEC), *Vibrio cholerae*, and *Salmonella typhimurium*.⁶¹ HMOs promote interferon-gamma (INF- γ) and IL-10 expression, which protect infants from *rotavirus virus* infection, diarrhea, and constipation, and they increase beneficial species, such as *Bifidobacterium*.⁶² Galactooligosaccharides (GOS), which are similar to HMOs, combine galactosyl residues, and they have a terminal glucose end with a β -glycosidic linkage. Also, GOS have anti-inflammatory properties and increase the number of *Bifidobacterium* species,⁶³ which is similar to HMOs. β -Glucan is a fermentable fiber that maintains intestinal integrity by modulating the immune function and macrophage activation. It also reduces pathogen colonization and increases the natural killer cells' activity, shown in Fig. 1.

Fats

Fat is an essential macronutrient that is of great importance to a balanced diet.⁶⁴ Certain dietary lipids make it beyond the small intestine's digestion and into the colon, where the gut bacteria can metabolize them. Such fatty acid-based development reduces community members' synthesis of SCFAs and antioxidants, which may have detrimental health repercussions for the host. Dietary fat metabolism alters the condition of enteric infection and establishes the link between the host and their gut microbe against enteric pathogenic bacteria.⁶⁵ A comparative study of the differing fats that are present in milk (SCFAs), olive oil (medium-chain fatty acids), and fish oil (omega-3 fatty acid) found that these fats have anti-inflammatory activity, which include IL-10, IL-33, and SCFA, in mice after an acute *Citrobacter rodentium* challenge.⁶⁶ Another source of fat, coconut oil, has medium chain fatty acids, and it benefits health by reducing enteric infections of the intestine, which can also inhibit *Candida albicans*.^{67,68} A diet rich in adequate omega-3 fatty acids may infer antibacterial properties to the gut microbiota, inhibiting intracellular pathogens and providing a beneficial anti-inflammatory effect in the intestines. However, the excessive intake of omega-3 fatty acids during viral infection worsens the condition of the infection and contributes to the damaging effect, as shown in Fig. 2. Sources of beneficial fats, which include sunflower oil and canola oil, both induce a pro-inflammatory response, and they are essential in order to nullify the damaging effect of an infection and aid in the clearance of them.⁶⁹ A piglet study demonstrated that a mixed lipid combination of omega-3 fatty acid, fish oil, olive oil, and soybean conferred anti-inflammatory properties and cleared enteric infections better than soybean alone.⁷⁰ The branched-chain fatty acids isoleucine, leucine, and valine are the major components of casein and whey. Branched-chain fatty

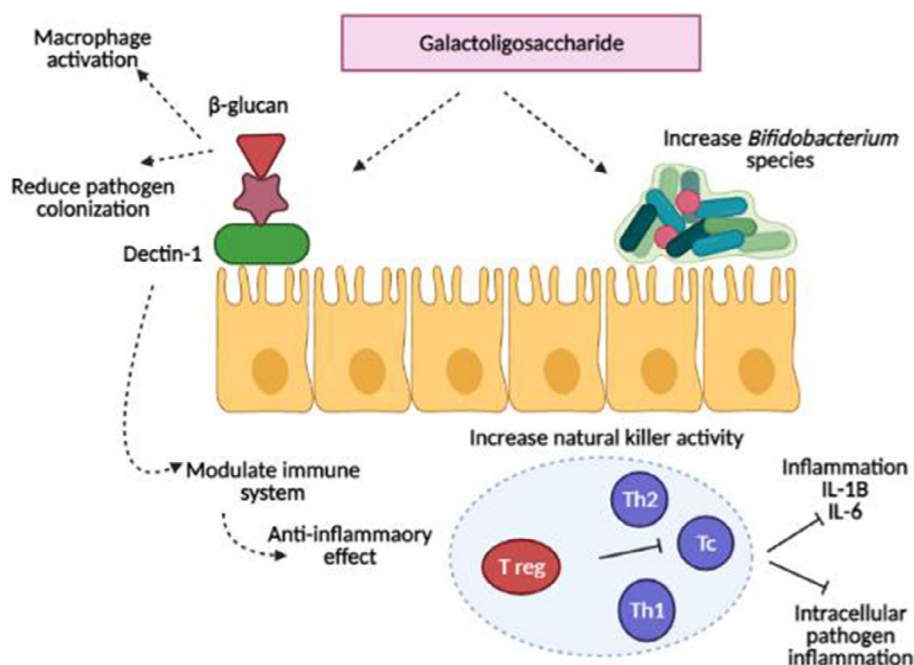


Figure 1. Role of galactooligosaccharides in maintaining intestinal integrity.

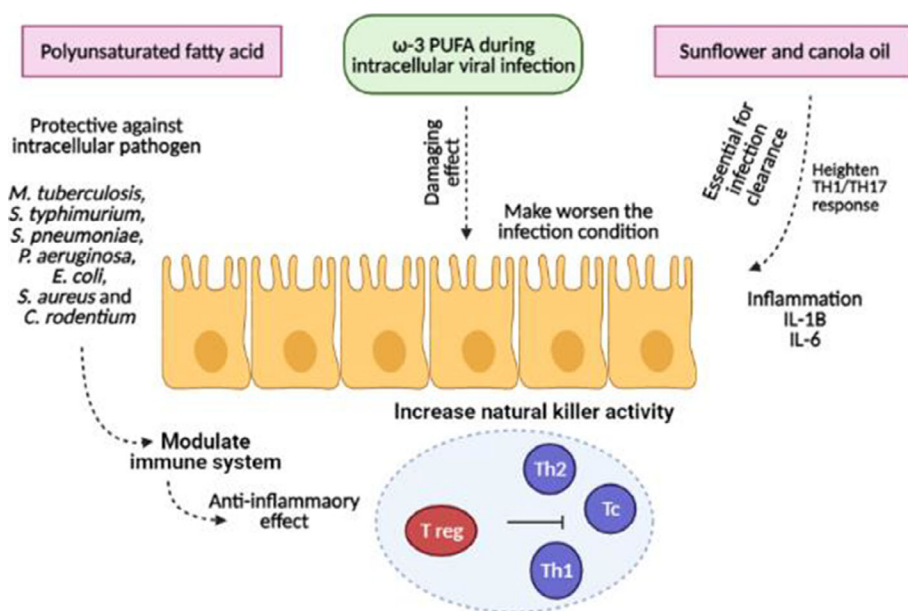


Figure 2. Effect of omega-3 fatty acid during the intracellular viral infection.

acids also increase the populations of *Akkermansia* and *Bifidobacterium*, which may also contribute to the weight management effect.⁷¹

High-fat diet

According to the World Health Organization (WHO) guidelines, a diet with adequate fat levels, such as saturated fat, should be less than 10% of total energy intake, and trans-fat, less than 1% of total energy intake, may provide some health benefits.⁷² However, excessive fat consumption is associated with the perturbation of gut homeostasis and can contribute to several metabolic disorders. The consumption of high levels of fat specifically contributes

to a leaky gut, which leads to the permeability of toxic metabolite excretions by bacterial dysbiosis, and it subsequently causes various associated disorders. Crohn's disease (CD) is related to excessive fat consumption. The development of CD is particularly associated with high fat levels and particular compositions of a high-fat diet. High-fat diets shift the microbiota in CD patients, enhancing the mucin-degrading bacteria *Ruminococcus torques* and increasing a specific group of bacteria, *Bacteroides/Prevotella*. High-fat diets also promoted *Escherichia coli* colonization in carcinoembryonic antigen-related cell adhesion molecule (CEACAM)-expressing mice.⁷³ This diet affects host homeostasis, and it alters the commensal bacteria populations, which allows for the

colonization of adherent invasive *Escherichia coli* in intestinal mucus and induces immunity mediators, such as C-reactive protein, leptin, resistin, TNF- α , and IL-6 that leads to CVD. A high-fat diet generally reduces the intestinal barrier function, which increases the immune response and promotes Th17-biased immunity that is observed in obese people.⁷⁴

Proteins

Proteins are essential macronutrients that maintain the body's basic metabolic functions. Compounds found in protein-rich foods result in microbial responses that are specific to each compound's unique nature, and the gut microbiome responds to changing proteolytic fermentation, which are the immune and metabolic responses to the amino acid metabolism. Protein deficiency impairs all metabolic activities and weakens the immune response against enteric infection. Adequate protein consumption is essential for tissues.⁷⁵ Protein malabsorption impairs tissue repair in parasitic *cryptosporidium* infection.⁷⁶

Excessive protein consumption, in contrast, encourages the growth of proteolytic bacteria and interferes with the host's functions. For example, lysine and proline encourage streptococci in order to utilize the growth of Clostridia, tryptophan, and glutamate, and aromatic amino acids encourage the growth of *Enterobacter* and *Escherichia* spp.⁷⁷

A diet with adequate protein consumption has been suggested in order to promote weight management and control. A balanced amount of carbohydrates and protein can more importantly override the path towards obesity or prevent it. The branched-chain fatty acids, which include isoleucine, leucine, and valine, are the major components of casein and whey. The high consumption of branched-chain fatty acids increases energy expenditure and contributes to the observed anti-obesity effect. Branched-chain fatty acids also increase the populations of *Akkermansia* and *Bifidobacterium*, which may also contribute to the weight management effect.⁷¹ Mice fed with an obesogenic diet, such as pork, chicken, and crab, which are abundant sources of taurine, have a negative correlation with body mass, so it is believed that taurine has a preventive effect on obesity. Increased amounts of taurine can help achieve gut homeostasis by decreasing the proteobacteria, such as *Helicobacter*, which is followed by increasing the concentration of SCFAs.⁷⁸ Seafood that contains aromatic amino acids and n-3 polyunsaturated fatty acids and meat that has saturated fatty acids are, in contrast, responsible for endocannabinoid production, and they facilitate the intake and storage of energy, which induces obesity in mice. Studies that were conducted on beef-derived protein and its effect on gut bacteria found decreases in the *Akkermansia* and *Bifidobacterium* communities and increases in the *Blautia* and *Clostridia* communities.⁷⁹

Abundant amount of protein in the diet produces branched-chain fatty acids, ammonia, amines, phenol, *p*-cresol, indole, and hydrogen sulfide (H₂S). These metabolites are responsible for the proliferation of intestinal inflammation, and they contribute to rectum and colon cancer, which take root in the lowest portions of the digestive tract.⁷⁷ In contrast, the production of SCFAs and abundant fiber fermentation protects against colorectal cancer and reduces intestinal inflammation. A high casein diet leads to dextran sulfate sodium colitis due to an increase in the density of microbes and a related decrease in the diversity of microbes.⁸⁰ Colonization was seen in a comparative study even after 3 days of infection, when a high dietary crude protein, such as wheat and casein was fed to weaned pigs that were infected with enterotoxigenic *Escherichia coli* K88. In contrast, no colonization

of enterotoxigenic *Escherichia coli* K88 was found after 3 days of infection, which was due to the corresponding decrease in proteolytic fermentation,⁸¹ when low crude fibers were fed to the same pigs. This suggests that low crude protein reduces the *Escherichia coli* K88 colonization on the mucosal surface of weaned piglet plant-based protein, such as soybean products, peanuts, pistachios, chickpeas, and fava beans, which contained less digestible detrimental isoflavone, and they can therefore contribute to higher rates of endotoxemia, a decreased immune response, and an increase in parasitic oocyst fecal output.⁸² For example, fish, chicken, pork, beef, and casein, which are animal-sourced protein, are highly digestible compared with plant-based protein foods, and they lead to lower rates of endotoxemia.⁸³ Beneficial *Lactobacilli* species increase with white protein, including fish and chicken, to promote gut health, whereas red proteins threaten gut health.⁸³

Dietary glutamine supplements restore intestinal integrity by enhancing intestinal cell proliferation, which decreases the firmicutes population and activates innate immunity via NF- κ B, MAPK, and P13k-Akt pathways.⁸⁴ Arginine supplements have a similar effect as glutamine, and they decrease the firmicutes population, including species from the genus *Dialister*, *Dorea*, *Pseudobutyribrio*, and *Veillonella*.⁵⁷ Glutamine and arginine restore the microbial balance, which reduces the pathogenic loads, and they recover the damaging effects of irritable bowel syndrome. Gut permeability and inflammation are lowered by dietary glutamine supplementation.⁸⁵

Phytochemicals

Phytochemicals are biologically active compounds that are found in various parts of plants, which include roots, seeds, leaves, bark, flowers, and fruit, and many of them have been reported to possess antimicrobial, anti-inflammation, and antioxidant properties that can protect against stress, pathogenic predation, and infection.⁸⁶ A subset of phytochemicals, polymeric flavanols tannins, have antinutritional properties that reduce nutrient utilization, impairing GIT integrity and decreasing metabolic function.⁸⁷ The consumption of these phytochemicals reduces digestibility by inhibiting enzymatic activity and protein precipitation.⁸⁸ However, phytochemicals can have beneficial effects on the host's metabolic function and the gut microbiome. The liver reintroduces phytochemicals via the enterohepatic circulation to microbes, so it is treated as a xenobiotic. This reintroduction of phytochemicals can strengthen the host's immunity and aid in pathogenic resistance.⁸⁹ Naringenin, which is a flavorless and colorless flavanone, acts against the aryl hydrocarbon receptor (AhR) and induces regulatory T cells, which can consequently suppress allergy autoimmune disorders.⁹⁰ Indole-3-carbinol conversely acts as an AhR ligand, and it contributes to the anti-inflammatory response (IL-22), which protects against *Clostridium difficile* infection.⁹¹ Phytochemicals are non-nutritional and physiologically active components that can alter the composition of gut microflora in the intestine. These chemicals have positive effects on the gut microbial population, which is due to their slow absorption. Feeding phytochemical-rich foodstuffs to humans and animals may provide a way to improve the gut microbiota, which results in improved performance, health, and wellbeing.⁹²

Cranberry extract has an anti-adhesive property that limits the ability of pathogenic *Escherichia coli* and *Proteus mirabilis* to attach to the host cells.⁹³ The cranberry extract polyphenolic flavan-3-ol binds to the host cells and inhibits the alternative binding of pathogens, such as pathogenic *Escherichia coli* adhesin (fimbriae).⁹³

A-type proanthocyanins protect against diet-induced obesity by inhibiting the lipase and glycosidase microbial enzymes.⁹⁴ Phyto-nutrient supplementations, such as garlic extract, anethol, capsicum oleoresin, eugenol, and cinnamaldehyde, alternatively increase beneficial *Clostridia* species and mucolytic bacteria. Positive feedback formed between mucolytic bacteria, such as *Akkermansia* sp. can degrade mucus O-linked glycans that increase SCFA production, stimulate goblet cells, and increase mucus secretion, which results in a thicker mucus layer.⁹⁵ In conjunction with other factors, this occurrence strengthens the mucosal barrier function and protects epithelial cells from invading pathogens and diseases. Pea seed coats are rich in B-type proanthocyanins, which contribute to the increased colonization of non-commensal bacteria, which decrease firmicutes populations, improper mucus formation, and increased mucin content.⁹⁶ Curcumin, which is an effective constituent of the *Curcuma longa*, has beneficial health effects, such as anti-proliferative, antioxidant, and anti-inflammatory properties. This compound suppresses the development of tumors, which increases the bacterial richness of *Lactobacillales* and decreases the order of *Coriobacteriales*.⁹⁷

Phenolic rich extracts

The recent literature discusses the impacts of dietary polyphenols by utilizing tea, wine, grapes, pomegranates, and berries. The consumption of 1000 mL/day of green tea for 10 days increases the Bifidobacteria count,⁹⁸ which provides an increase in the actinobacteria, firmicutes, enterococci, and klebsiella spp. ratios. *Akkermansia* spp. and a reduction in Bifidobacteria, *Blautia coccoides*, *Anaeroglobus* spp., and *Victivallis* spp. were apparent after the administration of black tea extract for 14 days.⁹⁹ The dark tea extricates enhanced in the thearubigins, which are 82% by weight of the tea flavonoids, have been displayed to apply a bifidogenic impact at a physiologically appropriate dosage. There is a reduction of Firmicutes/Bacteroidetes and *Bacteroides/Prevotella* ratio after consuming 500 mg/kg of fermented green tea extract in high-fat diet-fed rats for 8 weeks.¹⁰⁰ The tea oil administration increased the extent of *Erysipelotrichaceae* and *Lachnospiraceae* is also connected with fasting blood glucose, low-density lipoprotein, and total cholesterol level¹⁰¹ in another *in vivo* study.

It was found that the consumption of wine modulates the gut microbiota, which is due to the presence of phenolic compounds. These phenolic compounds include flavonoids, such as anthocyanidins, flavanols, flavones, and flavanols as well as non-flavonoids, such as hydrolysable tannins, phenolic acids, and stilbenes.¹⁰² Red wine utilization of 272 mL/day for 20 to 30 days in a human dietary mediation trial increased the number of inhabitants in *Bifidobacterium* spp. Red wine utilization additionally increases the number of *Bacteroides* spp., *Blautia coccoides*, *Eubacterium rectale* group, *Eggerthella lenta*, *Enterococcus* spp., *Prevotella* spp., and *Bacteroides uniformis*, and it diminishes the extents of the pathogenic *Clostridium histolyticum* group and *Clostridium* spp.¹⁰³ The phenolic compounds in grapes incorporate flavonoids and non-flavonoids,¹⁰⁴ which is like those found in wines. The medical advantages of grapes are being examined in ongoing investigations according to their interaction with gut microbiota and the ensuing administrative impacts of grape polyphenols on the colonic microbial environment.

The grapes seed extract obtained by batch culture fermentation pique *Enterococcus* spp. and *Lactobacillus* spp. growth reduces the number of pathogenic *Clostridium histolyticum* groups.¹⁰⁵ Grape pomace extricate was tried against bacterial growth of human

fecal matter in another study, and it displayed a stimulatory impact on the development of *Lactobacillus* spp., *Bacteroides*, *Enterobacteriaceae*, *Clostridium* group XIVa, and *Faecalibacterium prausnitzii*.¹⁰⁶ The pure culture incubation *in vitro* method with grape seed extract and its monomeric and oligomeric rich fraction provided the inhibitory effect to *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Lactobacillus vaginalis*, and *Streptococcus thermophilus*, even though it enhanced the growth of *Lactobacillus casei* and *Lactobacillus bulgaricus*.¹⁰⁷ The administration of 1% grape seed extract w/w for 6 days to pigs caused an increase in the number of unclassified *Clostridiales*, *Ruminococcaceae*, *Lachnospiraceae*, and *Lactobacillus*, and 3-hydroxybenzoic acid and 4-hydroxyphenylvaleric acid was also found as primary phenolic metabolites.¹⁰⁸ This review revealed that grape pomace extricates provoke the number of Bifidobacteria. However, they provoked a number of *Clostridium sensu stricto*, which is group I, seen in the control group, which was inhibited after the administration of grape pomace extract for 14 days. It was suggested that the drawn-out supplementation of grape pomace extricate that is rich in polyphenols may rebuild the rodent gut microbiota profile for a better aggregate.¹⁰⁹

Berries are relatively rich in phytochemicals compared with other foods, which are dominant in anthocyanins.¹¹⁰ The content and variety of anthocyanin species are variable factors among berries, and they are also dependent upon the ripening state of the berries. Investigations focused on the possible advantages of berry utilization and its consequences for the human gut microflora. There was an elevation of *Corynebacteria* spp., *Thermomonospora* spp., and *Slackia* spp. after the administration of lowbush wild blueberries in a mouse trial, which is in contrast to the reduction of *Enterococcus* spp. and *Lactobacillus* spp.¹¹¹ The supplementation of blueberry extract at 4 mL/kg body weight for 6 days enhanced the growth of beneficial bacteria, such as Bifidobacteria and Lactobacilli.¹¹²

Pomegranates contain a high percentage of phenolic compounds in various sections, which include peels, seeds, and juice. The vital content of pomegranate incorporates ellagitannins, flavonoids, phenolic acids, and proanthocyanins.¹¹³ The incubation of pomegranate extracts with bacteria found an increase in *Bifidobacterium infantis* and *Bifidobacterium breve*, which is in contrast to the inhibition of *Staphylococcus aureus*, *Clostridium perfringens*, and *Clostridium ramosum*¹¹⁴ in an *in vitro* study. Pure cultures that were incubated with pomegranate juice and extract were found to have a stimulatory effect on the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. in another study, which is contrary to the reduction in the growth of *Bacteroides fragilis*, *Clostridium* spp., and *Enterobacteriaceae*.¹¹⁵ A total of 12 healthy people were administered 200 mL of pomegranate juice each day for 4 weeks, and the profiling of the gut microbiota was analyzed using 16s rRNA sequencing. No considerable differences were observed in any of the fecal microbiotas.¹¹⁶

Vitamin and minerals

Minerals and vitamins contribute to necessary functions, such as maintaining proper metabolic activity and an activated immune response, and they are essential in growth, fluid balance, and bone health.¹¹⁷ Deficiency of these micronutrients leads to decreased Firmicutes, reduced mucus formation, and increased fecal mucin content. Significant deficits in micronutrients can negatively impact the host's health.¹¹⁸ Supplementation can counter some of these deficiencies. For example, zinc supplements reduce the common cold by 33%, and vitamin C

supplements reduce it by 14%.^{119,120} Copper and zinc have shown bactericidal activity by increasing the phagocytotic activity of intracellular pathogens.¹²¹ Zinc deficiency, in particular, leads to an impaired immune response, increasing the severity of infection and decreasing leukocyte infiltration.¹²²

Excessive iron supplementation, in contrast induces the production of radicals, which reduces the intestinal integrity and subsequently encourages the growth of intracellular pathogens.¹²³ However, neutrophils produce the lipocalin-2 protein during epithelial inflammation, interfering with the iron uptake with bacteria and leading to decreased pathogen overgrowth and severity. On the other spectrum of micronutrients, vitamins confer some protective effects on the host with adequate consumption via diet or supplementation. Vitamin B₁₂ is an essential nutrient that is required for the proper growth of bacteria. Commensal bacteroides *thetaitaomicon* compete for this vitamin B₁₂, which opposes enterohemorrhagic *Escherichia coli* colonization and reduces the Shiga type toxin, which improves general health.¹²⁴

Emulsifiers

Emulsifiers are chemical additives that stabilize mixtures, which can be found in many food products. Carboxyl methylcellulose and polysorbate 80 are emulsifiers that are commonly found in processed food, and they have been implicated in gut microbiota fluctuations, which lead to an increase in pro-inflammatory signals.¹²⁵ Continued low-grade inflammation due to these pro-inflammatory signals can lead to the onset of diseases, such as colitis. The increased consumption of emulsifiers, such as the emulsifiers in processed foods has been associated with decreased intestinal integrity by disturbing the mucus layer, which protects the epithelial cell layer from interactions with pathogenic bacteria that causes the onset of various metabolic disorders, such as hyperglycemia and obesity. Insulin resistance increased emulsification consumption and increased SCFA and bile acid levels, which in turn induces intestinal inflammation and epithelial permeability and promotes the disease condition.¹²⁶ Dietary emulsifiers also stimulate the invasive *Escherichia coli* gene expression progression and drive chronic intestinal inflammation.¹²⁷ The study shows that glycerol monolaurate (GML) is responsible for negatively altering the gut microbiota via increased *Escherichia coli* populations and decreased abundance of *Akkermansia muciniphila*.¹²⁸ Carrageenan, which is a sulfated polysaccharide emulsifier that is widely used in dairy products, such as yogurt, cottage cheese, ice cream, and some non-dairy desserts, caused intestinal microbiota fluctuations.¹²⁹ The consumption of food containing carrageenan is correlated with the induction of pro-inflammation markers in the gut,¹³⁰ and it is linked to various inflammation-related illnesses, such as leaky gut and CVD, obesity,¹²⁵ heart disease, and celiac disease,¹³¹ which prompted the United States Department of Agriculture (USDA) to remove carrageenan from the list of permissible food additives.¹³² However, not all emulsifiers are correlated with negative alterations in the gut microbiota. One study showed that combining xylanase and emulsifier positively modulated gut microbiota, reducing the clostridia community and not changing the *Lactobacilli* and *Bifidobacteria* populations.¹³³

Artificial sweeteners

Sugar substitutes are commonplace in the food industry, and there are currently five artificial sweeteners, which include saccharin, acesulfame, aspartame, neotame, and sucralose, approved by the US Food and Drug Administration (FDA). These sugar

substitutes have been shown to alter the microbial communities of mice, and they can contribute to glucose intolerance. Artificial sweeteners show increases in the populations of *Enterobacteriaceae*, *Deltaproteobacteria*, and *Actinobacteria* phyla.¹³⁴ Acidic cyclic sulfonamide (Acesulfame K), which is an artificial sweetener, has been found to increase the abundance of *Bacteroides* in male mice as well as reduce the abundance of *Lactobacillus* and *Clostridium* in female mice.¹³⁵ This same study also showed no significant changes in other community populations, which included *Anaerostipes* and *Sutterella*.¹³⁵ Another sweetener, aspartame, is a dipeptide that offers 200 times more sweetness than sucrose.¹³⁶ Aspartame consists of aspartic and phenylalanine, and it is rapidly metabolized, which produces metabolites, such as SCFAs. Aspartame increased in both the *Enterobacteriaceae* and *Clostridium leptum* communities.¹³⁷

Two other artificial sweeteners, Advantage and Neotame, have shown no substantial side effects on human health upon consumption, and both have been defined as non-toxic food additives.¹³⁸ These sweeteners move through the GIT without signs of accumulation.¹³⁹ Cyclamate, which is another additive, is approved and used in more than 50 European countries, but it has been removed by the FDA from the list of approved food additives. The consumption of cyclamate increased the sulfatase activity in the fecal samples,¹⁴⁰ and it altered the metabolic activity of gut microbiota in rats by reducing the fermentation rate of carbohydrates, which is a process that is key to microbial gut health.¹⁴¹ There is currently no data regarding the alteration of the human gut microbiota that concerns the consumption of these types of food additives.

Saccharin is a commonly used sweetening agent that is found in food and beverages. It is FDA-approved and considered a safe food additive, but this artificial sweetener has been linked to increased carcinogenic properties.¹⁴² However, the consumption of it can affect aerobic microbes, and it explicitly decreases the abundance of *Lactobacillus* species.¹⁴³ Saccharin also reduces the number of commensal bacteria, such as *Akkermansia muciniphila*, which exhibits beneficial probiotic properties for the gut microbiome and the host.¹⁴⁴ Its deleterious effect on metabolic activity is again worsened by additional antibiotic treatment and associated with harmful pro-inflammatory activity. Sucralose also appears to affect the anaerobic populations of microbes, which is unlike saccharin. Sprague Dawley rats, which were fed sucralose for 14 weeks, saw an alteration in the gut microbiota populations and specific decreases in the aerobic and anaerobic bacteria, which included *Bacteroides*, *Bifidobacteria*, *Clostridium*, and *Lactobacilli*,¹⁴⁵ were found.

Drugs

The specific composition of the gut microbiome can affect both the efficacy of and the response to drugs of the host. Metformin and berberine are used in order to assist with the recovery from diabetic conditions, and they have been shown to modulate the gut microbiota by increasing the SCFA-producing bacteria *Allobaculum*, *Bacteroides*, *Blautia*, *Butyrivibrio*, and *Phascolarctobacterium*.¹⁴⁶ The increase in SCFAs-producing bacteria and the resulting increased SCFA production improve the overall GIT health. Not all diabetic drugs positively affect the gut microbiota. Some of them can even negatively impact the gut microbiota.¹⁴⁷ It has been shown that the combination of antibiotics, probiotics, and prebiotics is involved in the modulation of structural components of the gut environment. Antimicrobials, which are targeted to kill bacteria, typically reduce the diversity of microorganisms in

Table 1. Effects of the dietary component to regulate gut health and microbiota

Factor(s)	Alteration(s)	Clinical relevance	Reference
Curcumin	Increased microbial diversity, decreased <i>Coriobacteriales</i> , and increased <i>Lactobacillales</i> . Colonic histology showed signs of progress. Higher survival and a lower weight-to-length ratio in the colon.	Improved in the condition of tumorigenesis.	151
Emulsifiers: carboxymethyl-cellulose and polysorbate-80	Levels of butyrate reduced and altered levels of bile acid. Results provide a new way of breaking down host-microbiota interactions and show that these widely used food additives might directly affect the microbiota.	Elevated risk of inflammation and altered the metabolic process.	152
High-fat diet	Decreased in bacteria diversity, <i>Bifidobacterium</i> (beneficial), and <i>Eubacterium</i> .	Increased production of nitrosamines (carcinogen) and inflammation.	36
Metformin and Berberine	Altered structural composition of gut microbes significantly reduced microbes' diversity, which are elevated in short-chain fatty acid (SCFA) producing bacteria. Both medications reversed the structural alterations in the gut microbiota caused by a high-fat diet.	Prevention of metabolic disease and the anti-obesity effect.	153
Polyphenols and proanthocyanins	Stimulation of the growth of beneficial microbes and reduction of pathogenic bacteria, prebiotic-like effects, and production of beneficial metabolites.	Improvement in immune-inflammatory diseases and chronic inflammatory and autoimmune diseases, such as inflammatory bowel disease.	154,155
Sweeteners (artificial)	Elevation in <i>Actinobacteria</i> phylum, <i>Deltaproteobacteria</i> , and <i>Enterobacteriaceae</i> . Reduction in <i>Bifidobacterium</i> , <i>Bacteroides</i> , <i>Lactobacillus</i> , and increased incretin secretion.	Glucose intolerance decreased motility and visceral hypersensitivity.	134
Omega-3 fatty acids.	Elevate species diversity and enrich the microbiota for probiotic-type bacteria.	Reduced the risk of heart disease and cancer.	156,157

the gut and open niches for the enhanced growth of pathogenic bacteria, such as *Clostridium difficile*.¹⁴⁸

Drugs, such as digoxin, which control heart problems, irinotecan, which treat cancer, and L-DOPAM, which treat Parkinson's disease, reduce metabolic diseases by modulating the gut bacteria.¹⁴⁹ Metronidazole and vancomycin are typically used to treat diarrhea and colitis, and they are specifically used in order to reduce the disease-causing bacteria *Clostridium difficile*. Metronidazole and vancomycin are often ineffective in ridding the host of this pathogen due to the spore-forming property of *Clostridium difficile*. The resistance of *Clostridium difficile* and the antibiotic-induced microbial population decrease, metronidazole, and vancomycin can worsen the gut condition.¹⁵⁰ Regulation of gut health and microbiota through dietary components is shown in Table 1. Additionally, the role of probiotics in mitigation of diseases and through their possible mechanistic route is summarized in Table 2.

GENETICALLY MODIFIED PROBIOTICS

Probiotics are known as therapeutic strategies for various diseases, but they are not universally accepted due to a lack of data and understating. The modification of probiotics is growing to be used for specific metabolite production or to increase the activity of probiotics.¹⁷⁸ Genetically modified probiotics can be the safest therapeutic tool in order to modulate the gut microbiota and reduce the number of pathogenic microorganisms. It is a novel therapy that involves a beneficial microorganism that can be safe.¹⁷⁹ There is presently an increase in awareness about the gut microbiota being responsible for healthy or diseased

conditions. Hence, bioengineered microbes or probiotics treat the disease or deliver vaccines.¹⁸⁰ It is also used as a biomarker in order to detect inflammation, as the vehicle for vaccination, as a receptor mimics, to enhance the immune system, and to destroy toxins and pathogens.¹⁸¹ Probiotic bacteria, such as *Lactobacillus* and *Bifidobacteria*, are responsible for modulating gut microbiota and reducing GIT infection.¹⁸²

PROBIOTIC VERSUS GENETICALLY MODIFIED PROBIOTICS

Human gut microbiota may vary in regards to the individual and incorporate friendly and pathogenic bacteria that maintain the symbiotic relationship. Various factors can disturb the symbiotic relationship of gut flora and cause lifestyle disorders. Factors that affect the gut microflora include lifestyle, diet, aging, stress, and climate change, which can lead to various health issues.¹⁸³ As a result, the researchers are now focusing on improving gut microbiota with bioengineered technology. Probiotics can produce antimicrobial compounds, such as bacteriocin and organic acid, that can inhibit the growth of pathogenic bacteria. Most probiotics are consumed as food components that can withstand bile acid stress and can be part of the GIT. The main concern about probiotics is their survival in stressful conditions, such as high pH, low and high temperature, and the oxygen concentration. Probiotics can be encapsulated and added to food in order to protect from stress conditions, which increases the survivability of probiotics in food and reduces the damage caused by the external environment.¹⁸⁴ The sensory acceptance of probiotic products is another alarming factor. There is a need to develop genetically

Table 2. The role of probiotics in the mitigation of diseases and their possible mechanistic route

Probiotics strain	Disease name	Model	Action of mechanism	References
<i>Lactobacillus salivarius</i> CUL61, <i>Lactobacillus paracasei</i> CUL08, <i>Bifidobacterium animalis</i> subspecies lactis CUL34 and <i>Bifidobacterium</i> <i>bifidum</i> CUL20	Eczema.	Pregnant women and their infants.	Probiotic prevent atopic sensitization to common food allergens and so reduce the incidence of atopic eczema in early childhood.	158
<i>Lactobacillus rhamnosus</i> GG <i>Escherichia</i> <i>coli</i>	Food allergies.	Pediatric patients, preterm infant.	Probiotic administration likely results in inducing tolerance among infants with suspected allergy.	159,160
VSL#3 <i>Bacillus circulans</i> PB7	Immunity.	Mouse model, catla catla.	Probiotic treatment attenuates sickness behavior development in mice with liver inflammation without affecting disease severity, gut microbiota composition, or gut permeability.	161,162
<i>Lactobacillus acidophilus</i> NCFM, ATCC 700396; <i>Lactobacillus paracasei</i> Lpc- 37, ATCC SD5275; <i>Bifidobacterium</i> <i>lactis</i> Bi-07, ATCC SC5220; <i>Bifidobacterium lactis</i> B1-04, ATCC SD5219.	<i>Clostridium</i> <i>difficile</i> infection (CDI).	Human.	Probiotic use may impact the microbiome function in the face of a CDI.	163
<i>Lactobacillus rhamnosus</i> and <i>Lactobacillus helveticus</i>	Gastroenteritis therapeutics.	Children.	Probiotics, defined as viable microbial preparations that have a beneficial effect on the health of the host.	164
<i>Lactobacillus crispatus</i> CTV-05, <i>Lactobacillus rhamnosus</i> GR-1 <i>Lactobacillus reuteri</i> RC-14	Vaginal candidiasis (thrush).	Women	Vaginal concentration of certain bacterial vaginosis-associated bacteria, vaginal intercourse during treatment and presence of endogenous <i>Lactobacillus crispatus</i> at enrollment predict colonization with probiotic <i>Lactobacilli</i> .	165,166
<i>Lactobacillus reuteri</i> RC-14, <i>Lactobacillus</i> <i>rhamnosus</i> GR-1, <i>Lactobacillus</i> <i>rhamnosus</i> GG, <i>Bifidobacterium</i> BB-12 <i>Lactobacillus rhamnosus</i> GR-1 <i>Lactobacillus reuteri</i> RC-14	Urinary tract infection (UTI).	Human.	Probiotics are shown to be effective in preventing UTI and multi-resistant organism colonization, they would be a very attractive alternative for UTI prophylaxis.	167,168
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium</i> sp., <i>Lactobacillus</i> <i>acidophilus</i>	Lactose intolerance.	Lactose intolerance patients (human).	After probiotic intervention, the hydrogen level was lower in experimental group in comparison with the control group. Lactose intolerance symptoms in the experimental group were much less than the control group.	169
<i>Bifidobacterium longum</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium lactis</i> , <i>Lactobacillus</i> <i>acidophilus</i> , <i>Lactobacillus rhamnosus</i> , and <i>Streptococcus thermophilus</i> , <i>Saccharomyces</i>	Irritable bowel syndrome (IBS).	IBS patients.	Multispecies probiotics are effective in IBS patients and induce alterations in intestinal microbiota composition.	170,171
<i>Lactobacillus plantarum</i> 299v, <i>Lactobacillus</i> GG	Traveler's diarrhea.	Caco-2 cell, randomized, double-blinded, placebo- controlled conditions.	Probiotics can play an important role in reducing the secretory change in response to enteropathogenic <i>Escherichia coli</i> (EPEC) infection, possibly through inhibition of its binding. However, the presence of the probiotic agent before the infection is necessary. In this setting, its role is more preventive rather than therapeutic.	172,173
<i>Escherichia coli</i> strain Nissle 191, <i>Bifidobacterium</i> , <i>Lactobacillus</i>	Crohn's disease.	Patients with Crohn's disease.	Probiotics exhibited dose- and time-dependent adherence to intestinal epithelial cells and inhibited the adhesion and invasion of various adherent-invasive <i>Escherichia coli</i> strains	174,175
	Ulcerative colitis.	Rat	Treatment with probiotic resulted in significant reduction in serum levels of C-reactive protein,	176,177

Table 2. Continued

Probiotics strain	Disease name	Model	Action of mechanism	References
<i>Lactobacillus acidophilus</i> , <i>Escherichia coli</i> Nissle 1917, <i>Bifidobacterium</i> , <i>Lactobacillus fermentum</i>			TNF- α and IL-6, as well as disease activity index (DAI). Probiotic could be recommended as adjuvant therapy to achieve more effective treatment for ulcerative colitis.	

modified probiotics that can survive in stressful environments and benefit human health due to the limitations of conventional probiotics.¹⁸⁵

Genetically modified probiotics, which is in contrast to antibiotics, can lead to a reduction in non-pathogenic bacteria and result in the development of antibiotic resistance in humans.¹⁸⁶ The treatment of antibiotics leads to the emergence of resistant microbes, which is due to a reduction in the valuable microorganisms.¹⁸⁷ These need the development of bioengineered probiotics, which are genetically modified and produce the antimicrobial compound, mucosal delivery of peptides, cytokine, allergens, DNA, and enzymes.¹⁸⁸

UTILIZATION OF GENETICALLY MODIFIED PROBIOTICS

Anticarcinogen

The treatment of cancer can cause an increase in the resistance of anticarcinogen, which has led to finding alternative approaches that do not raise the resistance condition. One alternative therapy is recombinant probiotics that can multiply in tumor cells and cope with cancer, such as clostridia species.¹⁸⁹ Engineering strains to produce a prodrug-converting enzyme (PCE), which precisely transforms a non-toxic prodrug into a cytotoxic drug at the tumor site, can enhance the anti-tumor activity. Using this method, the effectiveness of *Clostridium*-Directed Enzyme Prodrug Therapy (CDEPT) was shown in a mouse xenograft model of human colon cancer. Many animals were healed and there was significant tumor suppression. These positive results imply that a potential platform for the clinical development of CDEPT is the innovative enzyme and strain engineering technique.¹⁸⁹ These probiotics specifically target the cancer cell that inhibits cancerous cell multiplication. The clostridia species was replaced by a genetically modified tumor-targeting variant, *Salmonella typhimurium* A1-R, to treat malignant cancers.¹⁹⁰ *Escherichia coli* Nissle 1917 is the non-pathogenic strain used for targeting tumor cells, which reproduces in tumor cells and causes cell necrosis, which leads to a reduction in cancerous cells.¹⁹¹ The manipulation strategies of probiotics or bacteria can emerge as novel tools in order to mitigate cancer. The delivery of bacteria to the targeted cancer cell is considered safe compared with the toxicity that is caused by drug treatments.¹⁹² Oncolytic viruses, including *Bifidobacteria*, *Clostridia*, *Escherichia coli*, *Salmonella*, and *Shigella*, are anaerobic facultative and obligate bacteria targeting the primary and metastatic melanomas.¹⁹³ The modified strain was able to colonize and detect the biomarker, use signaling pathways, develop various therapeutic compounds, and control anti-inflammatory effects in order to cure inflammatory intestinal diseases.¹⁸⁰

Antimicrobial

Bioengineered probiotics help in order to combat the resistance of antimicrobial drugs. They can specifically produce antimicrobial compounds, which are organic acids, such as lactic acid, bacteriocin, and lactic acid, and they kill the pathogen. The organic acid production by probiotics decreases the pH of the environment and inhibits or excludes pathogenic microorganisms. Largely, though not entirely, the antibacterial activity of lactic acid is attributed to its capacity to cross the cytoplasmic membrane in its undissociated state, which lowers intracellular pH and displaces the transmembrane proton motive force.¹⁹⁴ The improper use of antibiotics causes the bacteria to become antimicrobial resistant, which is multidrug resistance. These side effects of the drug can be overcome by using antimicrobial peptides. *Lactococcus lactis* is genetically modified with the gene A3APO, which releases the altyserin antimicrobial peptide that effectively works against *Salmonella* and *Escherichia coli*.¹⁹⁵ Bioengineered probiotics can produce antimicrobial peptides and kill the pathogen. The antimicrobial peptide can inhibit Gram-negative pathogenic bacteria, such as *Salmonella* and *Escherichia coli*. It is well known that the inner lipid bilayer membranes of Gram-positive and Gram-negative bacteria differ significantly from one another. Antimicrobial peptides of different classes work by binding to and permeabilizing these membranes.¹⁹⁵ The probiotic strain *Lactococcus lactis* strain IL1403 was bioengineered to produce antimicrobial peptides, which showed considerable activity against *Salmonella* and *Escherichia coli*.¹⁹⁶ This technique is unsuccessful due to its limitations, which include being time-consuming and costly, and it may have the possibility of being destroyed before it reaches the gut.

Immunomodulation

The vaccine is the biological preparation of attenuated pathogens that can reduce infectious diseases. An immunocompromised person may have a chance of reversion back to an attenuated pathogen and act as an infectious agent. This problem can be overcome by consuming genetically modified probiotics and directly transferring the immunogenic component to the mucosal surface.¹⁹⁷ Non-pathogenic food-grade lactic acid bacteria (LAB) might be employed as live antigen carriers as an alternative to this tactic. Therefore, LAB provide appealing substitutes as antigen carriers, and the development of mucosal vaccines has been the primary use for LAB. It can be an ideal vector in regards to transferring the immunogenic component to the mucosal surface, which directly contact the antigens and antibodies with the activation of the humoral and cell-mediated immune response by the colonization of genetically modified probiotics on the epithelial cell. An activated immune response acts against infectious agents and protects them from infections.¹⁹⁸ Interleukins have

subsequently been co-expressed with antigens in LAB to boost the body's defenses against the antigen. Additionally, LAB have been used as a delivery method for various compounds with various uses, including as anti-infectives, treatments for gastrointestinal disorders, and treatments for allergy illnesses.¹⁹⁸ A llama heavy-chain antibody that expresses *Lactobacillus paracasei* can act against the rotavirus. It binds to the rotavirus and reduces it in infected cell cultures, which is shown by enzyme-linked immunosorbent assay (ELISA) and scanning electron microscopy (SEM).¹⁹⁹ *Lactobacillus casei* protects the nasopharynx from *Streptococcus pneumoniae*. One of the studies of a *Lactobacillus casei* surface that expresses pneumoniae protein is responsible for nasal immunization and protection from pneumonia infection.¹⁹⁹ This commensal gut bacteria underwent transformation to produce recombinant strains that express a high density of rotavirus-specific sdAbs on their cell surface, which are known as lactobodies. Recombinant lactobacillus feeding also significantly prevented rotavirus-mediated illness. *Lactobacillus acidophilus* was genetically modified with the gag gene from the HIV1 with or without the co-expression of FliC in order to serve as a vector for the vaccine and elicit the immune response or protect against HIV.²⁰⁰ It is possible that the recombinant strain exhibiting FliC and Gag dual display will have a distinct immunopotency from the strain expressing Gag alone, as the surface-exposed flagellin maintained its TLR5-stimulating activity. Immunization against *Lactobacillus acidophilus* expressing both Gag and FliC increased the number of cells that secreted IgA specific to Gag. These findings revealed that the presence of FliC had an adjuvant impact on local IgA synthesis and that the Gag-displaying *Lactobacillus acidophilus* induced particular immune responses.

Neurological illness

Neurological disorders occur due to an imbalance of neurotransmitter levels in the brain, and they cause neurodegeneration that leads to reduced cognitive activity, such as learning, memory, and thinking. The probiotics that improve cognitive activity or maintain the gut-brain axis are called psychobiotics. This newly introduced group delivers neurotransmitters, such as GABA, serotonin, and dopamine.²⁰¹ The vagus nerve, spinal cord, or neuroendocrine systems may all play a role in mediating effects. These advantages could be connected to some psychobiotics' anti-inflammatory properties and their ability to lower hypothalamic–pituitary–adrenal axis activity. The probiotics are combined for essential neurotransmitter production in the gut. The gut is the nerve end of hundreds of millions of nerves, which modulate the brain's activity by the gut. The neurotransmitter-producing probiotics trigger the vagus nerve in order to transform neurotransmitters from the gut to the brain and improve cognitive activity. Improving neurological conditions with microbial-based tools can be used as a therapeutic approach. Several *in vivo* and *in vitro* studies confirm that metabolites produced by gut bacteria can improve brain metabolism.²⁰² Both normal reactions to stress and defense against the central consequences of illness and inflammation can be mediated by the microbes in the gut. The majority of behavioral effects that have been reported thus far are associated with stress, anxiety, and a changed response of the hypothalamus–pituitary–adrenal axis. LAB that can reduce neurotoxins, such as amines, ammonia, and indoles will enhance mood disorders.²⁰³

Stress resistance

Probiotics cannot tolerate stress conditions, such as high temperatures and high pH. The probiotics are modified in order to produce GroEL and GroES heat shock protein in all temperature conditions, which help them withstand the high temperatures.²⁰⁴ The stress tolerance capacity of probiotics increases via genetic modification, which is bioengineered. The transfer of pathogen genes to stress-tolerant bacteria or probiotics improves the tolerance of probiotics. The expression of heat shock protein chaperones improved the thermotolerant property. The stress tolerance of recombinant probiotics survived ten-fold better than the stress-adapted probiotics, and they survived 54-fold better than the non-adapted strains.²⁰⁵ Research indicates that cultures sensitive to technology, such as Lactobacilli that are probiotics, may be modified to become more resilient to survive in challenging environments, such as during the manufacture of food products or during gastrointestinal transit. The carnitine and betaine (bet) uptake genes encode for the salt-tolerant properties. *Listeria monocytogenes* possesses the betL gene, which the uptake of betaine increases the resistance to stress, such as osmotolerant, cryotolerant, and barotolerant.²⁰⁶ A risk–benefit analysis study can be used in order to evaluate the obtained gene product in stress tolerance.²⁰⁷

CONCLUSIONS

The interplay of the diet, which is the microbial populations that inhabit the digestive system, and the host is crucial in maintaining the host's health and preventing dysfunction and disease. The components of our diet are crucial in modulating the gut microbiome, and they are essential to promote immunity and resilience to metabolic diseases. A diet high in fiber, vitamins, and minerals can promote the populations of bacteria that have ameliorative action against metabolic disease. This host immunity to pathogenic bacteria is tightly linked to dietary influence and microbiota synergistic actions. Improved host intestinal integrity and infection resistance are achieved via the fermentation of undigested fiber and the downstream metabolites of the microbiome. Diet interventions with minerals, vitamins, fibers, antioxidants, protein, and low-calorie choices with limited source of n-6 polyunsaturated fatty acids protect our intestinal integrity. A balanced diet can mitigate the onset of various diseases that are related to gut dysbiosis and modulate the structure and population of the gut. Macronutrients and micronutrients in conjunction protect the GIT environment. The alteration of compromised gut microbiomes via consuming a good diet and a genetically modified organism can improve health outcomes via this modulation of the microbial population and its resultant protective effects. Moreover, the gut's environment particularly pH is vital in regards to deciding the population of the gut microbiota. This makes it pivotal to place a more prominent attempt in order to distinguish the scope of the microorganisms that might be provoked by a given genetically modified probiotics, carbohydrate, and non-carbohydrate diet approach. The improvement of diet that is planned in order to help the health of humans needs to assess the exceptionally individual species profiles, which include reasons of adequacy and wellbeing.

Probiotic microorganisms are presently gaining popularity, and researchers are incorporating conventional medicine into translational techniques in the 21st century. All of the key elements of health management, such as drug metabolism and identification,

toxicity, and the development of novel medicines are ultimately impacted by intestinal bacteria. It is possible to evaluate the combined advantages of genetically modified probiotics, which include their direct antagonistic reaction against pathogenic bacteria and the immunomodulatory potentials against malignancies, pathogenic bacteria, and metabolic illnesses. Recombinant probiotics are anticipated as a new class of treatments despite conflicting results about the recombinant microorganisms and their metabolites. Recombinant probiotics' repertoire of antibacterial, immunomodulatory, and anti-inflammatory properties may be particularly useful in the combination therapies strategy in order to treat infections and metabolic illnesses. Most of the research has thus far shown the advantages of synthetic probiotics in animal models, and the results of certain human clinical trials are highly encouraging. The three fundamental obstacles for genetically designed probiotics are the selection of probiotic strains, optimal dosing, and horizontal gene transfer from genetically modified probiotics to other bacterial species. Genetically modified probiotics are effective and innovative alternative medicines for treating infections and metabolic illnesses. Further studies should explore the human microbiota in order to develop prospective modified strains as alternative treatments. The engineered probiotics may be useful in order to restore health with ease, efficacy, and site specificity.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

- 1 Stecher B, The roles of inflammation, nutrient availability and the commensal microbiota in enteric pathogen infection. *Microbiol Spectr* **3**:1-17 (2015).
- 2 Andrew DP, Pedersen PM and McEvoy CD, *Research Methods and Design in Sport Management*. Human Kinetics, Illinois, USA, (2019).
- 3 Bäckhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM *et al.*, Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. *Cell Host Microbe* **12**:611-622 (2012).
- 4 Ma T, Shen X, Shi X, Sakandar HA, Quan K, Li Y *et al.*, Targeting gut microbiota and metabolism as the major probiotic mechanism—an evidence-based review. *Trends Food Sci Technol* **138**:178-198 (2023).
- 5 Koh A, De Vadder F, Kovatcheva-Datchary P and Bäckhed F, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell* **165**:1332-1345 (2016).
- 6 Zmora N, Suez J and Elinav E, You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol* **16**:35-56 (2019).

- 7 Pellizzon MA and Ricci MR, Effects of rodent diet choice and fiber type on data interpretation of gut microbiome and metabolic disease research. *Curr Protoc Toxicol* **77**:e55 (2018).
- 8 Monack DM, Mueller A and Falkow S, Persistent bacterial infections: the interface of the pathogen and the host immune system. *Nat Rev Microbiol* **2**:747-765 (2004).
- 9 Vlasova AN, Takanashi S, Miyazaki A, Rajashekara G and Saif LJ, How the gut microbiome regulates host immune responses to viral vaccines. *Curr Opin Virol* **37**:16-25 (2019).
- 10 Singh RK, Chang HW, Yan DI, Lee KM, Ucmak D, Wong K *et al.*, Influence of diet on the gut microbiome and implications for human health. *J Transl Med* **15**:1-17 (2017).
- 11 Kovatcheva-Datchary P, Shoaie S, Lee S, Wahlström A, Nookaew I, Hallen A *et al.*, Simplified intestinal microbiota to study microbe-diet-host interactions in a mouse model. *Cell Rep* **26**:3772-3783 (2019).
- 12 Rey FE, Gonzalez MD, Cheng J, Wu M, Ahern PP and Gordon JL, Metabolic niche of a prominent sulfate-reducing human gut bacterium. *Proc Natl Acad Sci* **110**:13582-13587 (2013).
- 13 Mountzouris KC, Nutritional strategies targeting the beneficial modulation of the intestinal microflora with relevance to food safety: the role of probiotics and prebiotics, in *Food Safety: A Practical and Case Study Approach*. Springer US, Boston, MA, pp. 133-152 (2007).
- 14 Roy D, Technological aspects related to the use of bifidobacteria in dairy products. *Milk* **85**:39-56 (2005).
- 15 Peng M, Tabashum Z, Anderson M, Truong A, Houser AK, Padilla J *et al.*, Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. *Compr Rev Food Sci Food Saf* **19**:1908-1933 (2020).
- 16 Rossi F, Amadoro C and Colavita G, Members of the lactobacillus genus complex (LGC) as opportunistic pathogens: a review. *Microorganisms* **7**:126 (2019).
- 17 Olawale AK, David OM, Oluyeye AO, Osuntuyinbo RT, Laleye SA and Famurewa O, Histopathological changes induced in an animal model by potentially pathogenic enterococcus faecalis strains recovered from ready-to-eat food outlets in Osun state. *Nigeria Infect Drug Resist* **8**:181-187 (2015).
- 18 Mercenier A, Pavan S and Pot B, Probiotics as biotherapeutic agents: present knowledge and future prospects. *Curr Pharm Des* **9**:175-191 (2003).
- 19 Vieira AT, Fukumori C and Ferreira CM, New insights into therapeutic strategies for gut microbiota modulation in inflammatory diseases. *Clin Transl Immunol* **5**:e87 (2016).
- 20 Lakshmanan AP, Deola S and Terranegra A, The promise of precision nutrition for modulation of the gut microbiota as a novel therapeutic approach to acute graft-versus-host disease. *Transplantation* **10**:1097:2497-2509 (2023).
- 21 Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K *et al.*, Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. *Gut* **65**:63-72 (2016).
- 22 Blaser MJ and Falkow S, What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol* **7**:887-894 (2009).
- 23 Kau AL, Ahern PP, Griffin NW, Goodman AL and Gordon JL, Human nutrition, the gut microbiome and the immune system. *Nature* **474**:327-336 (2011).
- 24 Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M *et al.*, Human gut microbiome viewed across age and geography. *Nature* **486**:222-227 (2012).
- 25 Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM *et al.*, Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**:1470-1481 (2008).
- 26 Yeşilyurt N, Yılmaz B, Ağagündüz D and Capasso R, Microbiome-based personalized nutrition as a result of the 4.0 technological revolution: a mini literature review. *Process Biochem* **121**:257-262 (2022).
- 27 Stewart ML, Timm DA and Slavin JL, Fructooligosaccharides exhibit more rapid fermentation than long-chain inulin in an in vitro fermentation system. *Nutr Res* **28**:329-334 (2008).
- 28 Leitzmann C, Vegetarian nutrition: past, present, future. *Am J Clin Nutr* **100**:496S-502S (2014).
- 29 Nielsen LV, Kristensen MD, Klingenberg L, Ritz C, Belza A, Astrup A *et al.*, Protein from meat or vegetable sources in meals matched for fiber content has similar effects on subjective appetite

- sensations and energy intake—a randomized acute cross-over meal test study. *Nutrients* **10**:96 (2018).
- 30 Bouvard V, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L et al., Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* **16**:1599–1600 (2015).
- 31 Kim MS, Hwang SS, Park EJ and Bae JW, Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. *Environ Microbiol Rep* **5**:765–775 (2013).
- 32 Ashok AD, Kayalvizhi K and Ravivarman J, Indian vegetable diet in immunity development against viral diseases. *Int J Curr Microbiol App Sci* **9**:3411–3417 (2020).
- 33 Abdolghaffari AH, Farzaei MH, Lashgari NA, Roudsari NM, Haddadi NS, Singh AK et al., Dietary fiber and aging, in *Nutrients and Nutraceuticals for Active & Healthy Ageing*. Springer, Singapore, pp. 111–145 (2020).
- 34 Sofi F, Cesari F, Abbate R, Gensini GF and Casini A, Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* **337**:a1344 (2008).
- 35 Barrea L, Muscogiuri G, Frias-Toral E, Laudisio D, Pugliese G, Castellucci B et al., Nutrition and immune system: from the Mediterranean diet to dietary supplementary through the microbiota. *Crit Rev Food Sci Nutr* **61**:3066–3090 (2021).
- 36 Del Chierico F, Vernocchi P, Dallapiccola B and Putignani L, Mediterranean diet and health: food effects on gut microbiota and disease control. *Int J Mol Sci* **15**:11678–11699 (2014).
- 37 Lopez-Legarrea P, Fuller NR, Martinez JA, Caterson ID and Zulet MA, The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state. *Asia Pac J Clin Nutr* **23**:360–368 (2014).
- 38 Cardoso Dal Pont G, Farnell M, Farnell Y and Kogut MH, Dietary factors as triggers of low-grade chronic intestinal inflammation in poultry. *Microorganisms* **8**:139 (2020).
- 39 Venter C, Eyerich S, Sarin T and Klatt KC, Nutrition and the immune system: a complicated tango. *Nutrients* **12**:818 (2020).
- 40 Kurotani K, Akter S, Kashino I, Goto A, Mizoue T, Noda M et al., Japan public health center based prospective study group. Quality of diet and mortality among Japanese men and women: Japan public health center based prospective study. *BMJ* **352**:1–11 (2016).
- 41 D'Orazio N, Gemello E, Gammona MA, De Girolamo M, Ficoneri C and Riccioni G, Fucoxanthin: a treasure from the sea. *Mar Drugs* **10**:604–616 (2012).
- 42 Calviello G, Serini S and Piccioni E, n-3 polyunsaturated fatty acids and the prevention of colorectal cancer: molecular mechanisms involved. *Curr Med Chem* **14**:3059–3069 (2007).
- 43 Bougnoux P, Hajjaji N, Maheo K, Couet C and Chevalier S, Fatty acids and breast cancer: sensitization to treatments and prevention of metastatic re-growth. *Prog Lipid Res* **49**:76–86 (2010).
- 44 Gu Z, Suburu J, Chen H and Chen YQ, Mechanisms of omega-3 polyunsaturated fatty acids in prostate cancer prevention. *Biomed Res Int* **2013**:1–10 (2013).
- 45 Lima A, Oliveira J, Saúde F, Mota J and Ferreira RB, Proteins in soy might have a higher role in cancer prevention than previously expected: soybean protein fractions are more effective MMP-9 inhibitors than non-protein fractions, even in cooked seeds. *Nutrients* **9**:201 (2017).
- 46 Nagata C, Mizoue T, Tanaka K, Tsuji I, Takakoshi A, Matsuo K et al., Research Group for the Development and Evaluation of cancer prevention strategies in Japan. Soy intake and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* **44**:282–295 (2014).
- 47 Paoli A, Mancin L, Bianco A, Thomas E, Mota JF and Piccini F, Ketogenic diet and microbiota: friends or enemies? *Genes* **10**:534 (2019).
- 48 Omodei D and Fontana L, Calorie restriction and prevention of age-associated chronic disease. *FEBS Lett* **585**:1537–1542 (2011).
- 49 Rawat K, Singh N, Kumari P and Saha L, A review on preventive role of ketogenic diet (KD) in CNS disorders from the gut microbiota perspective. *Rev Neurosci* **32**:143–157 (2021).
- 50 Dupont A, Heinbockel L, Brandenburg K and Horneff MW, Antimicrobial peptides and the enteric mucous layer act in concert to protect the intestinal mucosa. *Gut Microbes* **5**:761–765 (2014).
- 51 Schroeder BO, Ehmann D, Precht JC, Castillo PA, Küchler R, Berger J et al., Paneth cell α -defensin 6 (HD-6) is an antimicrobial peptide. *Mucosal Immunol* **8**:661–671 (2015).
- 52 Ashaolu TJ, Immune boosting functional foods and their mechanisms: a critical evaluation of probiotics and prebiotics. *Biomed Pharmacother* **130**:110625 (2020).
- 53 Ağagündüz D, Cocozza E, Cemali Ö, Bayazit AD, Nani MF, Cerqua I et al., Understanding the role of the gut microbiome in gastrointestinal cancer: a review. *Front Pharmacol* **14**:1130562 (2023).
- 54 Mergenthaler P, Lindauer U, Dienel GA and Meisel A, Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci* **36**:587–597 (2013).
- 55 Marten AL and Garabaccio R, An applied general equilibrium model for the analysis of environmental policy: SAGE v1.0 technical documentation (2018).
- 56 Collins J, Robinson C, Danhof H, Knetsch CW, Van Leeuwen HC, Lawley TD et al., Dietary trehalose enhances virulence of epidemic *Clostridium difficile*. *Nature* **553**:291–294 (2018).
- 57 de Souza AZ, Zamboni AZ, Abboud KY, Reis SK, Tannihão F, Guadagnini D et al., Oral supplementation with L-glutamine alters gut microbiota of obese and overweight adults: a pilot study. *Nutrition* **31**:884–889 (2015).
- 58 Kumar J, Sharma P, Mitra MD, Sangwan S and Singh H, Molecular impact of dietary fibre metabolites on intestinal immunity of host, in *Immunology of the GI Tract-Recent Advances*. Intech Open, London, UK, (2022).
- 59 Andreas NJ, Kampmann B and Le-Doare KM, Human breast milk: a review on its composition and bioactivity. *Early Hum Dev* **91**:629–635 (2015).
- 60 Andersson B, Porras O, Hanson LÅ, Lagergård T and Svanborg-Edén C, Inhibition of attachment of *Streptococcus pneumoniae* and *Haemophilus influenzae* by human milk and receptor oligosaccharides. *J Infect Dis* **153**:232–237 (1986).
- 61 Manthey CF, Autran CA, Eckmann L and Bode L, Human milk oligosaccharides protect against enteropathogenic *E. coli* (EPEC) attachment in vitro and EPEC colonization in suckling mice. *J Pediatr Gastroenterol Nutr* **58**:165–168 (2014).
- 62 Correa-Matos NJ, Donovan SM, Isaacson RE, Gaskins HR, White BA and Tappenden KA, Fermentable fiber reduces recovery time and improves intestinal function in piglets following *Salmonella typhimurium* infection. *J Nutr* **133**:1845–1852 (2003).
- 63 Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G and Gibson GR, Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *Am J Clin Nutr* **88**:1438–1446 (2008).
- 64 Agans R, Gordon A, Kramer DL, Perez-Burillo S, Rufán-Henares JA and Paliy O, Dietary fatty acids sustain the growth of the human gut microbiota. *Appl Environ Microbiol* **84**:e01525 (2018).
- 65 Abulizi N, Quin C, Brown K, Chan YK, Gill SK and Gibson DL, Gut mucosal proteins and bacteriome are shaped by the saturation index of dietary lipids. *Nutrients* **11**:418 (2019).
- 66 DeCoffe D, Quin C, Gill SK, Tasnim N, Brown K, Godovannyi A et al., Dietary lipid type, rather than total number of calories, alters outcomes of enteric infection in mice. *J Infect Dis* **213**:1846–1856 (2016).
- 67 Gunsalus KT, Tornberg-Belanger SN, Matthan NR, Lichtenstein AH and Kumamoto CA, Manipulation of host diet to reduce gastrointestinal colonization by the opportunistic pathogen *Candida albicans*. *MSphere* **1**:10–1128 (2016).
- 68 Shilling M, Matt L, Rubin E, Visitation MP, Haller NA, Grey SF et al., Antimicrobial effects of virgin coconut oil and its medium-chain fatty acids on *Clostridium difficile*. *J Med Food* **16**:1079–1085 (2013).
- 69 Husson MO, Ley D, Portal C, Gotttrand M, Hueso T, Desseyn JL et al., Modulation of host defence against bacterial and viral infections by omega-3 polyunsaturated fatty acids. *J Infect* **73**:523–535 (2016).
- 70 Lavalley CM, Wizzard PR, Lansing M, Vine DF, Nation PN, Yap JY et al., Surgical anatomy does not affect the progression of intestinal failure-associated liver disease in neonatal piglets. *J Parenter Enteral Nutr* **42**:14–23 (2018).
- 71 Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS et al., An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* **63**:727–735 (2014).
- 72 Pereira RA, Duffey KJ, Sichieri R and Popkin BM, Sources of excessive saturated fat, trans fat and sugar consumption in Brazil: an analysis of the first Brazilian nationwide individual dietary survey. *Public Health Nutr* **17**:113–121 (2014).
- 73 Agus A, Denizot J, Thévenot J, Martinez-Medina M, Massier S, Sauvanet P et al., Western diet induces a shift in microbiota

- composition enhancing susceptibility to adherent-invasive *E. coli* infection and intestinal inflammation. *Sci Rep* **6**:19032 (2016).
- 74 Brown K, DeCoffe D, Molcan E and Gibson DL, Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* **4**:1095–1119 (2012).
 - 75 Jonker MA, Hermesen JL, Sano Y, Heneghan AF, Lan J and Kudsk KA, Small intestine mucosal immune system response to injury and the impact of parenteral nutrition. *Surgery* **151**:278–286 (2012).
 - 76 Bartelt LA, Bolick DT, Kolling GL, Roche JK, Zaenker EI, Lara AM *et al.*, Cryptosporidium priming is more effective than vaccine for protection against cryptosporidiosis in a murine protein malnutrition model. *PLoS Negl Trop Dis* **10**:e0004820 (2016).
 - 77 Diether NE and Willing BP, Microbial fermentation of dietary protein: an important factor in diet-microbe-host interaction. *Microorganisms* **7**:19 (2019).
 - 78 Yu H, Guo Z, Shen S and Shan W, Effects of taurine on gut microbiota and metabolism in mice. *Amino Acids* **48**:1601–1617 (2016).
 - 79 Albracht-Schulte K, Islam T, Johnson P and Moustaid-Moussa N, Systematic review of beef protein effects on gut microbiota: implications for health. *Adv Nutr* **12**:102–114 (2021).
 - 80 Llewellyn SR, Britton GJ, Contijoch EJ, Vennaro OH, Mortha A, Colombel JF *et al.*, Interactions between diet and the intestinal microbiota alter intestinal permeability and colitis severity in mice. *Gastroenterology* **154**:1037–1046 (2018).
 - 81 Opapeju FO, Krause DO, Payne RL, Rademacher M and Nyachoti CM, Effect of dietary protein level on growth performance, indicators of enteric health, and gastrointestinal microbial ecology of weaned pigs induced with postweaning colibacillosis. *J Anim Sci* **87**:2635–2643 (2009).
 - 82 Ford JT, Wong CW and Colditz IG, Effects of dietary protein types on immune responses and levels of infection with *Eimeria vermiformis* in mice. *Immunol Cell Biol* **79**:23–28 (2001).
 - 83 Zhu Y, Lin X, Zhao F, Shi X, Li H, Li Y *et al.*, Meat, dairy and plant proteins alter bacterial composition of rat gut bacteria. *Sci Rep* **5**:15220 (2015).
 - 84 Wei Q, Yang J, Ren J, Wang A, Ji T and Su Y, Bioactive phthalides from *Ligusticum sinense* Oliv cv. Chaxiong. *Fitoterapia* **93**:226–232 (2014).
 - 85 Bortoluzzi C, Rochell SJ and Applegate TJ, Threonine, arginine, and glutamine: influences on intestinal physiology, immunology, and microbiology in broilers. *Poult Sci* **97**:937–945 (2018).
 - 86 Moharram BA, Al-Mahbashi HM, Saif-Ali RI and AliAqlan F, Phytochemical, anti-inflammatory, antioxidant, cytotoxic and antibacterial study of *Capparis cartilaginea* decne from yemen. *Int J Pharm Sci* **10**:38–44 (2018).
 - 87 Muhammad Q, Gilani SN, Shahid F, Abdur R, Rifat N and Samreen P, Preliminary comparative phytochemical screening of euphorbia species. *Am-Eurasian J Agric Environ Sci* **12**:1056–1060 (2012).
 - 88 Pandey KB and Rizvi SI, Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev* **2**:270–278 (2009).
 - 89 Lillehoj H, Liu Y, Calsamiglia S, Fernandez-Miyakawa ME, Chi F, Cravens RL *et al.*, Phytochemicals as antibiotic alternatives to promote growth and enhance host health. *Vet Res* **49**:1–18 (2018).
 - 90 Wang J, Yang Z, Lin L, Zhao Z, Liu Z and Liu X, Protective effect of naringenin against lead-induced oxidative stress in rats. *Biol Trace Elem Res* **146**:354–359 (2012).
 - 91 Julliard W, De Wolfe T, Fechner JH, Safdar N, Agni R and Mezrich JD, Amelioration of *Clostridium difficile* disease in mice by dietary supplementation with indole-3-carbinol. *Ann Surg* **265**:1183–1191 (2017).
 - 92 Santhiravel S, Bekhit AE, Mendis E, Jacobs JL, Dunshea FR, Rajapakse N *et al.*, The impact of plant phytochemicals on the gut microbiota of humans for a balanced life. *Int J Mol Sci* **23**:8124 (2022).
 - 93 Nicolosi D, Tempera G, Genovese C and Furneri PM, Anti-adhesion activity of A2-type proanthocyanidins (a cranberry major component) on uropathogenic *E. coli* and *P. mirabilis* strains. *Antibiotics* **3**:143–154 (2014).
 - 94 Jobu K, Yokota J, Yoshioka S, Moriyama H, Murata S, Ohishi M *et al.*, Effects of Goishi tea on diet-induced obesity in mice. *Food Res Int* **54**:324–329 (2013).
 - 95 Wlodarska M, Willing BP, Bravo DM and Finlay BB, Phytonutrient diet supplementation promotes beneficial clostridia species and intestinal mucus secretion resulting in protection against enteric infection. *Sci Rep* **5**:9253 (2015).
 - 96 Forgie AJ, Gao Y, Ju T, Pepin DM, Yang K, Gänzle MG *et al.*, Pea polyphenolics and hydrolysis processing alter microbial community structure and early pathogen colonization in mice. *J Nutr Biochem* **67**:101–110 (2019).
 - 97 Sanlier N, Kocabas S, Erdogan K and Sanlier NT, Effects of curcumin, its analogues, and metabolites on various cancers: focusing on potential mechanisms. *Food Rev Int* **1**:21:5356–5376 (2022).
 - 98 Jin JS, Touyama M, Hisada T and Benno Y, Effects of green tea consumption on human fecal microbiota with special reference to Bifidobacterium species. *Microbiol Immunol* **56**:729–739 (2012).
 - 99 Kemperman RA, Gross G, Mondot S, Possemiers S, Marzorati M, Van de Wiele T *et al.*, Impact of polyphenols from black tea and red wine/grape juice on a gut model microbiome. *Food Res Int* **53**:659–669 (2013).
 - 100 Seo DB, Jeong HW, Cho D, Lee BJ, Lee JH, Choi JY *et al.*, Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. *J Med Food* **18**:549–556 (2015).
 - 101 Lin R, He X, Chen H, He Q, Yao Z, Li Y *et al.*, Oil tea improves glucose and lipid levels and alters gut microbiota in type 2 diabetic mice. *Nutr Res* **57**:67–77 (2018).
 - 102 Stockley C, Teissedre PL, Boban M, Di Lorenzo C and Restani P, Bio-availability of wine-derived phenolic compounds in humans: a review. *Food Funct* **3**:995–1007 (2012).
 - 103 Queipo-Ortuño MI, Boto-Ordóñez M, Murri M, Gomez-Zumaquero JM, Clemente-Postigo M, Estruch R *et al.*, Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am J Clin Nutr* **95**:1323–1334 (2012).
 - 104 Kennedy JA, Saucier C and Glories Y, Grape and wine phenolics: history and perspective. *Am J Enol Vitic* **57**:239–248 (2006).
 - 105 Cueva C, Sánchez-Patán F, Monagas M, Walton GE, Gibson GR, Martín-Álvarez PJ *et al.*, In vitro fermentation of grape seed flavan-3-ol fractions by human faecal microbiota: changes in microbial groups and phenolic metabolites. *FEMS Microbiol Ecol* **83**:792–805 (2013).
 - 106 Ferreira-Lazarte A, Moreno FJ, Cueva C, Gil-Sánchez I and Villamiel M, Behaviour of citrus pectin during its gastrointestinal digestion and fermentation in a dynamic simulator (simgi®). *Carbohydr Polym* **207**:382–390 (2019).
 - 107 Tabasco R, Sánchez-Patán F, Monagas M, Bartolomé B, Moreno-Arribas MV, Peláez C *et al.*, Effect of grape polyphenols on lactic acid bacteria and bifidobacteria growth: resistance and metabolism. *Food Microbiol* **28**:1345–1352 (2011).
 - 108 Choy YY, Quifer-Rada P, Holstege DM, Frese SA, Calvert CC, Mills DA *et al.*, Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. *Food Funct* **5**:2298–2308 (2014).
 - 109 Chacar S, Itani T, Hajal J, Saliba Y, Louka N, Faivre JF *et al.*, The impact of long-term intake of phenolic compounds-rich grape pomace on rat gut microbiota. *J Food Sci* **83**:246–251 (2018).
 - 110 Beattie J, Crozier A and Duthie GG, Potential health benefits of berries. *Curr Nutr Food Sci* **1**:71–86 (2005).
 - 111 Lacombe A, Tadepalli S, Hwang CA and Wu VC, Phytochemicals in lowbush wild blueberry inactivate *Escherichia coli* O157:H7 by damaging its cell membrane. *Foodborne Pathog Dis* **10**:944–950 (2013).
 - 112 Molan AL, Lila MA, Mawson J and De S, In vitro and in vivo evaluation of the prebiotic activity of water-soluble blueberry extracts. *World J Microbiol Biotechnol* **25**:1243–1249 (2009).
 - 113 Viuda-Martos M, Fernández-López J and Pérez-Álvarez JA, Pomegranate and its many functional components as related to human health: a review. *Compr Rev Food Sci Food Saf* **9**:635–654 (2010).
 - 114 Bialonska D, Kasimsetty SG, Khan SI and Ferreira D, Urolithins, intestinal microbial metabolites of pomegranate ellagitannins, exhibit potent antioxidant activity in a cell-based assay. *J Agric Food Chem* **57**:10181–10186 (2009).
 - 115 Li Z, Summanen PH, Komoriya T, Henning SM, Lee RP, Carlson E *et al.*, Pomegranate ellagitannins stimulate growth of gut bacteria in vitro: implications for prebiotic and metabolic effects. *Anaerobe* **34**:164–168 (2015).
 - 116 Mosele JI, Macià A, Romero MP, Motilva MJ and Rubió L, Application of in vitro gastrointestinal digestion and colonic fermentation models to pomegranate products (juice, pulp and peel extract) to study the stability and catabolism of phenolic compounds. *J Funct Foods* **14**:529–540 (2015).
 - 117 Basu TK and Donaldson D, Intestinal absorption in health and disease: micronutrients. *Best Pract Res Clin Gastroenterol* **17**:957–979 (2003).
 - 118 Goldenberg RL, The plausibility of micronutrient deficiency in relationship to perinatal infection. *J Nutr* **133**:1645S–1648S (2003).
 - 119 Hemilä H, Fitzgerald JT, Petrus EJ and Prasad A, Zinc acetate lozenges may improve the recovery rate of common cold patients: an

- individual patient data meta-analysis, in *Open Forum Infectious Diseases*, Vol. 4. Oxford University Press, US, p. ofx059 (2017).
- 120 Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P et al., Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. *Evid Based Complement Alternat Med* **2018**:5813095 (2018).
- 121 Djoko KY, Cheryl-lynn YO, Walker MJ and McEwan AG, The role of copper and zinc toxicity in innate immune defense against bacterial pathogens. *J Biol Chem* **290**:18954–18961 (2015).
- 122 Suliburska J, Skrypnik K, Szulińska M, Kupsz J, Markuszewski L and Bogdański P, Diuretics, Ca-antagonists, and angiotensin-converting enzyme inhibitors affect zinc status in hypertensive patients on monotherapy: a randomized trial. *Nutrients* **10**:1284 (2018).
- 123 Kortman GA, Boleij A, Swinkels DW and Tjalsma H, Iron availability increases the pathogenic potential of salmonella typhimurium and other enteric pathogens at the intestinal epithelial interface. *PLoS One* **7**:e29968 (2012).
- 124 Cordonnier C, Le Bihan G, Emond-Rheault JG, Garrivier A, Harel J and Jubelin G, Vitamin B12 uptake by the gut commensal bacteria *Bacteroides thetaiotaomicron* limits the production of shiga toxin by enterohemorrhagic *Escherichia coli*. *Toxins* **8**:14 (2016).
- 125 Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE et al., Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* **519**:92–96 (2015).
- 126 Dudek-Wicher RK, Junka A and Bartoszewicz M, The influence of antibiotics and dietary components on gut microbiota. *Prz Gastroenterol* **13**:85–92 (2018).
- 127 Viennois E, Bretin A, Dubé PE, Maue AC, Dauriat CJ, Barnich N et al., Dietary emulsifiers directly impact adherent-invasive *E. coli* gene expression to drive chronic intestinal inflammation. *Cell Rep* **33**:108229 (2020).
- 128 Jiang Z, Zhao M, Zhang H, Li Y, Liu M and Feng F, Antimicrobial emulsifier—glycerol monolaurate induces metabolic syndrome, gut microbiota dysbiosis, and systemic low-grade inflammation in low-fat diet fed mice. *Mol Nutr Food Res* **62**:1700547 (2018).
- 129 David S, Wojciechowska A, Portmann R, Shpigelman A and Lesmes U, The impact of food-grade carrageenans and consumer age on the in vitro proteolysis of whey proteins. *Food Res Int* **130**:108964 (2020).
- 130 Borthakur A, Bhattacharyya S, Anbazhagan AN, Kumar A, Dudeja PK and Tobacman JK, Prolongation of carrageenan-induced inflammation in human colonic epithelial cells by activation of an NF- κ B-BCL10 loop. *Biochim Biophys Acta Mol Basis Dis* **1822**:1300–1307 (2012).
- 131 Fahoum L, Moscovici A, David S, Shaoul R, Rozen G, Meyron-Holtz EG et al., Digestive fate of dietary carrageenan: evidence of interference with digestive proteolysis and disruption of gut epithelial function. *Mol Nutr Food Res* **61**:1600545 (2017).
- 132 Greger M, Should Carrageenan be avoided. *NutritionFacts.org.Blog* (2014).
- 133 Kubiś M, Kołodziejski P, Pruszyńska-Oszmałek E, Sassek M, Konieczka P, Górka P et al., Emulsifier and xylanase can modulate the gut microbiota activity of broiler chickens. *Animals* **10**:2197 (2020).
- 134 Spencer M, Gupta A, Van Dam L, Shannon C, Menees S and Chey WD, Artificial sweeteners: a systematic review and primer for gastroenterologists. *J Neurogastroenterol Motil* **22**:168–180 (2016).
- 135 Bian X, Chi L, Gao B, Tu P, Fu H and Lu K, The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. *PLoS One* **12**:e0178426 (2017).
- 136 Glaser D, Van Der Wel H, Brouwer JN, Dubois GE and Hellekant G, Gustatory responses in primates to the sweetener aspartame and their phylogenetic implications. *Chem Senses* **17**:325–335 (1992).
- 137 Palmnäs MS, Cowan TE, Bomhof MR, Su J, Reimer RA, Vogel HJ et al., Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat. *PLoS One* **9**:e109841 (2014).
- 138 Kallscheuer N, Engineered microorganisms for the production of food additives approved by the European Union—a systematic analysis. *Front Microbiol* **9**:1746 (2018).
- 139 Mitchell H ed, *Sweeteners and Sugar Alternatives in Food Technology*. John Wiley & Sons, West Sussex, UK, (2008).
- 140 Goldin BR, Intestinal microflora: metabolism of drugs and carcinogens. *Ann Med* **22**:43–48 (1990).
- 141 Pfeffer M, Ziesenitz SC and Siebert G, Acesulfame K, cyclamate and saccharin inhibit the anaerobic fermentation of glucose by intestinal bacteria. *Z Ernährungswiss* **24**:231–235 (1985).
- 142 Weihrauch MR and Diehl V, Artificial sweeteners—do they bear a carcinogenic risk? *Ann Oncol* **15**:1460–1465 (2004).
- 143 Daly K, Darby AC, Hall N, Nau A, Bravo D and Shirazi-Beechey SP, Dietary supplementation with lactose or artificial sweetener enhances swine gut lactobacillus population abundance. *Br J Nutr* **111**:S30–S35 (2014).
- 144 Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O et al., Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* **514**:181–186 (2014).
- 145 Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, McLendon RE and Schiffman SS, Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J Toxicol Environ Health A* **71**:1415–1429 (2008).
- 146 Stackebrandt E and Osawa R, Phascolarctobacterium, in *Bergey's Manual of Systematics of Archaea and Bacteria*, Vol. 1–4. Wiley, New Jersey (2015).
- 147 Montandon SA and Jornayvaz FR, Effects of antidiabetic drugs on gut microbiota composition. *Genes* **8**:250 (2017).
- 148 Mulder M, Radjabzadeh D, Kieft-de Jong JC, Uitterlinden AG, Kraaij R, Stricker BH et al., Long-term effects of antimicrobial drugs on the composition of the human gut microbiota. *Gut Microbes* **12**:1791677 (2020).
- 149 Wallace BD, Roberts AB, Pollet RM, Ingle JD, Biernat KA, Pellock SJ et al., Structure and inhibition of microbiome β -glucuronidases essential to the alleviation of cancer drug toxicity. *Chem Biol* **22**:1238–1249 (2015).
- 150 Abujamel T, Cadnum JL, Jury LA, Sunkesula VC, Kundrapu S, Jump RL et al., Defining the vulnerable period for re-establishment of *Clostridium difficile* colonization after treatment of *C. difficile* infection with oral vancomycin or metronidazole. *PLoS One* **8**:e76269 (2013).
- 151 McFadden RM, Larmonier CB, Shehab KW, Midura-Kiela M, Ramalingam R, Harrison CA et al., The role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention. *Inflamm Bowel Dis* **21**:2483–2494 (2015).
- 152 Chassaing B, De Bodt J, Marzotari M, Van de Wiele T and Gewirtz AT, Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. *Gut* **66**:1414–1427 (2017).
- 153 Zhang X, Zhao Y, Xu J, Xue Z, Zhang M, Pang X et al., Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. *Sci Rep* **5**:14405 (2015).
- 154 Jacobs DM, Gaudier E, Duynhoven JV and Vaughan EE, Non-digestible food ingredients, colonic microbiota and the impact on gut health and immunity: a role for metabolomics. *Curr Drug Metab* **10**:41–54 (2009).
- 155 Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ and Queipo-Ortuño MI, Benefits of polyphenols on gut microbiota and implications in human health. *J Nutr Biochem* **24**:1415–1422 (2013).
- 156 Byerley LO, Samuelson D, Blanchard E IV, Luo M, Lorenzen BN, Banks S et al., Changes in the gut microbial communities following addition of walnuts to the diet. *J Nutr Biochem* **48**:94–102 (2017).
- 157 Sardecka I, Krogulska A and Toporowska-Kowalska E, The influence of dietary immunomodulatory factors on development of food allergy in children. *Postepy Dermatol Alergol* **34**:89–96 (2017).
- 158 Allen SJ, Jordan S, Storey M, Thornton CA, Gravenor MB, Garaiova I et al., Probiotics in the prevention of eczema: a randomised controlled trial. *Arch Dis Child* **99**:1014–1019 (2014).
- 159 Tan-Lim CS and Esteban-Ipae NA, Probiotics as treatment for food allergies among pediatric patients: a meta-analysis. *World Allergy Organ J* **11**:25 (2018).
- 160 Lodinová-Zádníková R, Cukrowska B and Tlaskalova-Hogenova H, Oral administration of probiotic *Escherichia coli* after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). *Int Arch Allergy Immunol* **131**:209–211 (2003).
- 161 D'Mello C, Ronaghan N, Zaheer R, Dickey M, Le T, MacNaughton WK et al., Probiotics improve inflammation-associated sickness behavior by altering communication between the peripheral immune system and the brain. *J Neurosci* **35**:10821–10830 (2015).
- 162 Bandyopadhyay P and Das Mohapatra PK, Effect of a probiotic bacterium *Bacillus circulans* PB7 in the formulated diets: on growth, nutritional quality and immunity of *Catla catla* (ham.). *Fish Physiol Biochem* **35**:467–478 (2009).
- 163 De Wolfe TJ, Eggers S, Barker AK, Kates AE, Dill-McFarland KA, Suen G et al., Oral probiotic combination of lactobacillus and Bifidobacterium

- alters the gastrointestinal microbiota during antibiotic treatment for *Clostridium difficile* infection. *PLoS One* **13**:e0204253 (2018).
- 164 Freedman SB, Williamson-Urquhart S, Schuh S, Sherman PM, Farion KJ, Gouin S *et al.*, Impact of emergency department probiotic treatment of pediatric gastroenteritis: study protocol for the PRO-GUT (probiotic regimen for outpatient gastroenteritis utility of treatment) randomized controlled trial. *Trials* **15**:170 (2014).
 - 165 Ngugi BM, Hemmerling A, Bukusi EA, Kikuvu G, Gikunju J, Shiboski S *et al.*, Effects of BV-associated bacteria and sexual intercourse on vaginal colonization with the probiotic *Lactobacillus crispatus* CTV-05. *Sex Transm Dis* **38**:1020–1027 (2011).
 - 166 Martinez RC, Franceschini SA, Patta MC, Quintana SM, Gomes BC, De Martinis EC *et al.*, Improved cure of bacterial vaginosis with single dose of tinidazole (2 g), *Lactobacillus rhamnosus* GR-1, and *Lactobacillus reuteri* RC-14: a randomized, double-blind, placebo-controlled trial. *Can J Microbiol* **55**:133–138 (2009).
 - 167 Lee BB, Toh SL, Ryan S, Simpson JM, Clezy K, Bossa L *et al.*, Probiotics [LGG-BB12 or RC14-GR1] versus placebo as prophylaxis for urinary tract infection in persons with spinal cord injury [ProSCIUTT]: a study protocol for a randomised controlled trial. *BMC Urol* **16**:1–8 (2016).
 - 168 Anukam K, Osazuwa E, Ahonkhai I, Ngwu M, Osemene G, Bruce AW *et al.*, Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect* **8**:1450–1454 (2006).
 - 169 Masoumi SJ, Mehrabani D, Saberfirooz M, Fattahi MR, Moradi F and Najafi M, The effect of yogurt fortified with *Lactobacillus acidophilus* and *Bifidobacterium* sp. probiotic in patients with lactose intolerance. *Food Sci Nutr* **9**:1704–1711 (2021).
 - 170 Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW *et al.*, Effect of multi-species probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol Hepatol* **29**:52–59 (2014).
 - 171 Niu HL and Xiao JY, The efficacy and safety of probiotics in patients with irritable bowel syndrome: evidence based on 35 randomized controlled trials. *Int J Surg* **75**:116–127 (2020).
 - 172 Michail S and Abernathy F, *Lactobacillus plantarum* reduces the in vitro secretory response of intestinal epithelial cells to enteropathogenic *Escherichia coli* infection. *J Pediatr Gastroenterol Nutr* **35**:350–355 (2002).
 - 173 Bausserman M and Michail S, The use of *Lactobacillus GG* in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr* **147**:197–201 (2005).
 - 174 Boudeau J, Glasser AL, Julien S, Colombel JF and Darfeuille-Michaud A, Inhibitory effect of probiotic *Escherichia coli* strain Nissle 1917 on adhesion to and invasion of intestinal epithelial cells by adherent-invasive *E. coli* strains isolated from patients with Crohn's disease. *Aliment Pharmacol Ther* **18**:45–56 (2003).
 - 175 Fujimori S, Tatsuguchi A, Gudis K, Kishida T, Mitsui K, Ehara A *et al.*, High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. *J Gastroenterol Hepatol* **22**:1199–1204 (2007).
 - 176 Abdin AA and Saeid EM, An experimental study on ulcerative colitis as a potential target for probiotic therapy by *Lactobacillus acidophilus* with or without "olsalazine". *J Crohns Colitis* **2**:296–303 (2008).
 - 177 Peran L, Camuesco D, Comalada M, Nieto A, Concha A, Adrio JL *et al.*, *Lactobacillus fermentum*, a probiotic capable to release glutathione, prevents colonic inflammation in the TNBS model of rat colitis. *Int J Colorectal Dis* **21**:737–746 (2006).
 - 178 Ahmed FE, Genetically modified probiotics in foods. *Trends Biotechnol* **21**:491–497 (2003).
 - 179 Olle B, Medicines from microbiota. *Nat Biotechnol* **31**:309–315 (2013).
 - 180 Barra M, Danino T and Garrido D, Engineered probiotics for detection and treatment of inflammatory intestinal diseases. *Front Bioeng Biotechnol* **8**:265 (2020).
 - 181 Amalaradjou MA and Bhunia AK, Bioengineered probiotics, a strategic approach to control enteric infections. *Bioengineered* **4**:379–387 (2013).
 - 182 Evvie SE, Huo GC, Igene JO and Bian X, Some current applications, limitations and future perspectives of lactic acid bacteria as probiotics. *Food Nutr Res* **61**:1318034 (2017).
 - 183 Boyington JE, Schoster B, Shreffler J, Martin KR and Callahan LF, Peer reviewed: Perceptions of individual and community environmental influences on fruit and vegetable intake, North Carolina, 2004. *Prev Chronic Dis* **6**:A04 (2009).
 - 184 Shah NP, Functional cultures and health benefits. *Int Dairy J* **17**:1262–1277 (2007).
 - 185 Culligan EP, Hill C and Sleator RD, Probiotics and gastrointestinal disease: successes, problems and future prospects. *Gut Pathog* **1**:19 (2009).
 - 186 Singh B, Mal G, Bharti D, Mohania D, Kumar M, Kumar Gautam S *et al.*, Probiotics in female reproductive health: paradigms, prospects and challenges. *Curr Womens Health Rev* **9**:235–244 (2013).
 - 187 Hwang IY, Koh E, Wong A, March JC, Bentley WE, Lee YS *et al.*, Engineered probiotic *Escherichia coli* can eliminate and prevent *Pseudomonas aeruginosa* gut infection in animal models. *Nat Commun* **8**:15028 (2017).
 - 188 Sandes S, Alvim L, Silva B, Acurcio L, Santos C, Campos M *et al.*, Selection of new lactic acid bacteria strains bearing probiotic features from mucosal microbiota of healthy calves: looking for immunobiotics through in vitro and in vivo approaches for immunoprophylaxis applications. *Microbiol Res* **200**:1–13 (2010).
 - 189 Heap JT, Theys J, Ehsaan M, Kubiak AM, Dubois L, Paesmans K *et al.*, Spores of *Clostridium* engineered for clinical efficacy and safety cause regression and cure of tumors in vivo. *Oncotarget* **5**:1761–1769 (2014).
 - 190 Hoffman RM, Back to the future: are tumor-targeting bacteria the next-generation cancer therapy? *Methods Mol Biol* **1317**:239–260 (2015).
 - 191 Brichacek B, Lagenaur LA, Lee PP, Venzon D and Hamer DH, In vivo evaluation of safety and toxicity of a *Lactobacillus jensenii* producing modified cyanovirin-N in a rhesus macaque vaginal challenge model. *PLoS One* **8**:e78817 (2013).
 - 192 Andreu D and Torrent M, Prediction of bioactive peptides using artificial neural networks. *Methods Mol Biol* **1260**:101–118 (2015).
 - 193 Chang WW and Lee CH, *Salmonella* as an innovative therapeutic anti-tumor agent. *Int J Mol Sci* **15**:14546–14554 (2014).
 - 194 Alakomi HL, Skytta E, Saarela M, Mattila-Sandholm T, Latva-Kala K and Helander IM, Lactic acid permeabilizes gram-negative bacteria by disrupting the outer membrane. *Appl Environ Microbiol* **66**:2001–2005 (2000).
 - 195 Volzing K, Borrero J, Sadowsky MJ and Kaznessis YN, Antimicrobial peptides targeting gram-negative pathogens, produced and delivered by lactic acid bacteria. *ACS Synth Biol* **2**:643–650 (2013).
 - 196 Mandal SM, Silva ON and Franco OL, Recombinant probiotics with antimicrobial peptides: a dual strategy to improve immune response in immunocompromised patients. *Drug Discov Today* **19**:1045–1050 (2014).
 - 197 Tarahomjoo S, Development of vaccine delivery vehicles based on lactic acid bacteria. *Mol Biotechnol* **51**:183–199 (2012).
 - 198 Wells JM and Mercenier A, Mucosal delivery of therapeutic and prophylactic molecules using lactic acid bacteria. *Nat Rev Microbiol* **6**:349–362 (2008).
 - 199 Pant N, Hultberg A, Zhao Y, Svensson L, Pan-Hammarström Q, Johansen K *et al.*, *Lactobacilli* expressing variable domain of llama heavy-chain antibody fragments (lactobodies) confer protection against rotavirus-induced diarrhea. *J Infect Dis* **194**:1580–1588 (2006).
 - 200 Kajikawa A, Zhang L, Long J, Nordone S, Stoeker L, LaVoie A *et al.*, Construction and immunological evaluation of dual cell surface display of HIV-1 gag and *Salmonella enterica* serovar typhimurium FliC in *Lactobacillus acidophilus* for vaccine delivery. *Clin Vaccine Immunol* **19**:1374–1381 (2012).
 - 201 Dinan TG, Stanton C and Cryan JF, Psychobiotics: a novel class of psychotropic. *Biol Psychiatry* **74**:720–726 (2013).
 - 202 Forsythe P, Kunze WA and Bienenstock J, On communication between gut microbes and the brain. *Curr Opin Gastroenterol* **28**:557–562 (2012).
 - 203 Ramezani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R and Raj DS, Role of the gut microbiome in uremia: a potential therapeutic target. *Am J Kidney Dis* **67**:483–498 (2016).
 - 204 Fayet O, Ziegelhoffer T and Georgopoulos C, The groES and groEL heat shock gene products of *Escherichia coli* are essential for bacterial growth at all temperatures. *J Bacteriol* **171**:1379–1385 (1989).
 - 205 Desmond C, Fitzgerald GF, Stanton C and Ross R, Improved stress tolerance of GroESL-overproducing *Lactococcus lactis* and probiotic *Lactobacillus paracasei* NFBC 338. *Appl Environ Microbiol* **70**:5929–5936 (2004).
 - 206 Sleator RD, Gahan CG, O'Driscoll B and Hill C, Analysis of the role of betL in contributing to the growth and survival of *Listeria monocytogenes* LO28. *Int J Food Microbiol* **60**:261–268 (2000).
 - 207 Li Z, Pei X, Yin S, Lang X, Zhao X and Qu GZ, Plant hormone treatments to alleviate the effects of salt stress on germination of *Betula platyphylla* seeds. *J Forest Res* **30**:779–787 (2019).