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Review

A review on microbiota: relation with diseases and nutrients role

Emel Oz,[1] Ayşegül Şimşek,[2] Melih Şimşek,[3] Nihal Tuncer,[4] Muharrem Bayrak,[5] Kenan Çadırcı,[5] Charles Brennan,[6,7] Mukul Kumar,[8] Charalampos Proestos,[9] Margaret Brennan,[10] Tahra Elobeid,[11] Maomao Zeng,[12,13] Igor Tomasevic,[14,15] Elif Ekiz[1] & Fatih Oz[1]*

1 Department of Food Engineering, Agriculture Faculty, Ataturk University, Erzurum 25240, Türkiye
2 Department of Midwifery, Faculty of Health Sciences, İstinye University, Zeytinburnu, İstanbul 34010, Türkiye
3 Department of Medical Oncology, Faculty of Medicine, Bezmialem Vakif University, Fatih, İstanbul 34093, Türkiye
4 Department of Nutrition and Dietetics, Faculty of Health Sciences, İstanbul Okan University, Tuzla, İstanbul 34959, Türkiye
5 Department of Internal Medicine, Erzurum Regional Training and Research Hospital, Health Sciences University, Erzurum 25240, Türkiye
6 RMIT University, School of Science, Melbourne 3001, Victoria, Australia
7 Riddet Institute, Palmerston North 4442, New Zealand
8 Department of Food Technology and Nutrition, Lovely Professional University, Phagwara Punjab, 144411, India
9 Laboratory of Food Chemistry, Department of Chemistry, School of Sciences, National and Kapodistrian University of Athens Zografou, Athens 15784, Greece
10 School of Science, Royal Melbourne Institute of Technology University, Melbourne 3000, Australia
11 Human Nutrition Department, College of Health Sciences, QU Health, Qatar University, Doha 2713, Qatar
12 State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi 214122, China
13 International Joint Laboratory on Food Safety, Jiangnan University, Wuxi 214122, China
14 Faculty of Agriculture, University of Belgrade, Belgrade 11080, Serbia
15 University of Life Sciences, Lublin 20-109, Poland

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Summary Microbiota plays an essential role in human development and body homeostasis. Individual and environmental variables influence the diversity of microbiota, which performs crucial biochemical activities in the human body and influences health status and disease in later years. Many diseases in adulthood may be prevented or treated if the relationship between the microbiome, nutrition, especially the immune system, and growth and development could be fully understood. For a healthy gut microbiota, the diet-related changes in the core microbiota must be long-lasting, achieving permanence in microbiota change. This process is possible by maintaining a sustainable diet and adhering to this diet for a long time. Therefore, this study reviewed the relationship between nutrition, microbiota, and various life-threatening diseases.

Keywords cancer, central nervous system, immune system, irritable bowel syndrome, microbiota, nutrition.

Introduction

Microbiota

Microbiota refers to the collection of living microorganisms in a specific environment and developed in the human body from birth that significantly varies at every stage of life, *i.e.*, fetal periods such as amniotic fluid, placenta, cord blood, meconium, mode of delivery, feeding with breast milk or formula, age, antibiotic use, physical activity level, nutritional habits, and environmental factors (Ficara *et al.*, 2020). It contains several compositions in different regions such as gut (*Lactobacillus, Actinobacteria, Enterobacteria, Firmicutes*, and *Streptococci*), skin (*Actinobacteria, Cyanobacteria, Proteobacteria, Bacteriodetes*, and *Firmicutes*), oral (*Firmicutes, Proteobacteria, Bacteriodetes,* and *Fusobacteria*), respiratory (*Actinobacteria, Firmicutes, Proteobacteria,* and *Bacteriodetes*), and vaginal (*Lactobacilli*), which are present in microbiome system (Hou *et al.*, 2022). This system is involved in maintaining human health and body balance by giving energy from food, stimulating growth hormones, communicating between bacteria, strengthening the immune system, preventing the colonisation of pathogens (Petrillo *et al.*, 2020; Song *et al.*, 2021). Additionally, it plays a role in intestinal epithelium shaping, strengthening the gut functioning, producing bioactive neurotransmitters metabolism activity, homeostasis, functional properties of adipose tissue, and immune system by interacting with

*Correspondent: E-mail: fatihoz@atauni.edu.tr

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different body systems, *i.e.*, paracrine, endocrine, and autocrine signalling system (Alagöz, 2017; Woźniak *et al.,* 2021; Kwon & Khan, 2022).

Additionally, microbiota maintains human health and homeostasis by having an impact on many of the body functions (Alagöz, 2017). The microbial diversity in the human body shows periodic differences according to age. Although the number of microorganisms in the newborn period is less than in adults, it varies in the period up to 3 years (first 1000 days) (Robertson *et al.,* 2019). In a study comparing the gut microbiota of 1–4 years old children with healthy adults, the adult microbiome was reported to be significantly more diverse than that of younger children (Ringel-Kulka *et al.,* 2013). Breast milk is the essential nutrient containing beneficial microorganisms (*Bacteroides*, *Bifidobacterium*, and *Clostridium spp*.) responsible for developing the infant's microbiota in the first years of life (Grier *et al.,* 2017; Ficara *et al.,* 2020). Adult-type microorganisms such as *Bacteroides, Prevotella, Ruminococcus, Clostridium,* and *Veillonella* take their place during the supplementary feeding period (Grier *et al.,* 2017). Later in life, *Bifidobacterium* and some lactic acid bacteria become dominant and help to maintain the microbiota (Tanaka & Nakayama, 2017). Diversity and change in the microbiota of the mother (adverse conditions during pregnancy, smoking, and alcohol use, nutrition, diseases, *etc.*), of the baby (delivery type, place, birth weight, genetics, diet, antibiotic use, *etc.*) and due to environmental exposure (exposure to bacteria, domestic or farm animals, social factors, geographical origin, *etc.*), can interact with each other (Ficara *et al.,* 2020).

Microbiota also helps in the biosynthesis of vitamins, lipids, and amino acids with the help of several biochemical pathways and the impact of metabolic genes, immune response stimulation, blood pressure control, energy metabolism, food fermentation, and blockage of- pathogenic activities (Hou *et al.,* 2022). The symbiotic, stability, and resilience interaction also occurs with the host's healthy microbiota (Ficara *et al.,* 2020). Numerous diseases such as cardiovascular diseases, cancer, inflammatory bowel diseases, diabetes mellitus, and chronic respiratory, kidney, and liver diseases occur when the microbiota are unhealthy due to the significant pathogens, *i.e.*, *Tannerella forsythia, Porphyromonas gingivalis, Fusobacterium nucleatum, Enterococcus faecalis, Escherichia coli, Bacteroides fragilis, Roseburia faecis, Faecalibacterium prausnitzzi, Clostridium coccoides, Eubacterium rectale, Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis, Rhodotorula mucilaginosa, Mycoplasma salivarium, Helicobacter pylori, Treponema denticola, Aggregatibacter actinomycetemcomitans, Gammaproteobacteria,* and *Erysipelotrichia,* (Hou *et al.,* 2022). The scientists have reported a positive relationship between microbiota and health issues such as the lipid metabolism process, reproductive process, gastrointestinal (GI) tract, and cardiological effect in the germ-free mice colonised with human microbiota. Another report observed that antibiotics such as ciprofloxacin, dicloxacillin, cefuroxime, cefotaxime, and clindamycin were given to mice shows colonisation resistance with the help of resistant bacteria (*E. coli* or *Enterococcus*) (Hertz *et al.,* 2020). A study has been conducted on mice microbiota and revealed the effect of the epithelial cell and stimulation on immune response (Macia *et al.,* 2012). A study was done to check the phenotype associated with microbiota and observed it works in several diseases caused by the genes, such as inflammatory bowel diseases (Crohn's disease and ulcerative colitis) (Nguyen *et al.,* 2015). It also contains bacteria, fungi, and viruses in the human gastroenteric tract. The gut bacteria also control several functions, such as the production of vitamins, immune response stimulation, food fermentation, and blockage of pathogenic activities (Hou *et al.,* 2022).

Effect of microbiota on life-threatening diseases

Microbiota has a greater impact on several diseases such as liver diseases, lung diseases, cardiovascular diseases, irritable bowel disease, obesity, tumour, and inflammation as shown in Fig. 1.

Gut microbiota and irritable bowel disease

Irritable Bowel Disease (IBD) is a widespread disease that causes changes in bowel habits due to various factors, such as environmental, dietary, genetic, and psychological factors that contribute to the pathogenesis of IBD (Tavakoli *et al.,* 2021). IBD has a prevalence of 7–21% worldwide, and no biochemical marker is used for diagnosis. Patients with IBD typically have the following laboratory test results: normal serum C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR) levels, and < 50 μg/g faecal calprotectin levels. Diagnosis of IBD and categorization of IBD patients into subgroups are based on the Rome IV criteria and the Bristol Stool Form Scale (BSFS), established in recent years (Poon *et al.,* 2022). The increased incidence of IBD in recent years caused a substantial increase in the health expenditures of developed countries such as the United States, United Kingdom, Italy, Australia, China, *etc.* In parallel, approximately 2 billion dollars are spent on IBD patients in a year in the U.S., and a 200-million-dollar budget is allocated to IBD patients in China. Severe intestinal symptoms experienced during the disease cause psychological problems, isolation from society, and a decrease in quality of life (Aziz *et al.,* 2021).

The highly heterogeneous microbial community rapidly adapts to chemical exposure, immunological response, and dietary changes. Changes that cause

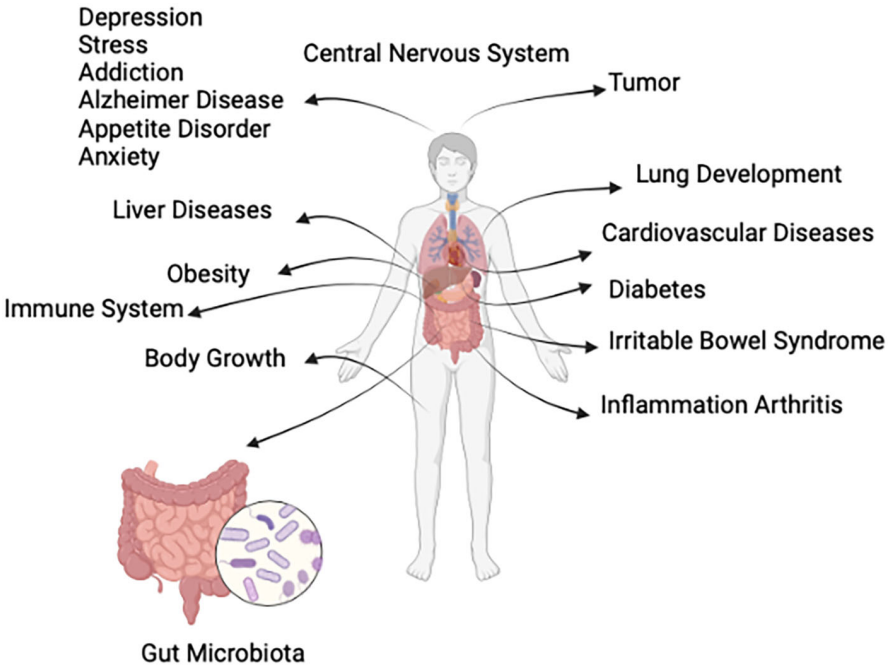

Figure 1 Impact of microbiota on life-threatening diseases.

disorders in the intestinal microbiota were reportedly associated with IBD experienced in the gastrointestinal tract. The decrease in bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium* in the intestinal microbiota is frequently observed in IBD patients (Chong *et al.,* 2019). Lactobacillus ensures mucosal protection by contributing to mucin production in the intestines by rapidly adhering to the intestinal epithelial cells (Staudacher *et al.,* 2021). *Campylobacter jejuni, Clostridium difficile, Escherichia coli, Helicobacter pylori,* and *Shigella* species may cause functional intestinal diseases such as IBD due to disruption of the intestinal mucosal barrier (Ghoshal, 2022). Especially, *H. pylori* are mainly responsible for gastric ulcer and cancer. Similarly, *H. pylori* are found in the normal intestinal epithelial mucosa. Recent studies have demonstrated that it causes systemic inflammation and hypersensitivity in the gastrointestinal tract. *Shigella* and *Salmonella* species induce IBD by strengthening the inflammatory response in the intestine and increasing gastrointestinal permeability (Feng *et al.,* 2021). It was reported in several studies published in recent years that certain psychological diseases, such as depression, contribute to the pathogenesis of IBD by affecting the neuronal, neuroendocrine, and neuroimmune pathways in the intestines. Disruptions in the intestinal mucosal barrier increase the pathogenic transfer of bacterial cells and toxins to the human body, affecting the hypothalamic–pituitary–adrenal axis and leading to an excessive immune response (Donoso *et al.,* 2022). Bacteroidetes affect the synthesis of serotonin and thus cause an increase in many symptoms, such as abdominal pain in IBD patients. Another critical factor that affects the intestinal microbiota is the circadian rhythm (Thaiss *et al.,* 2014). Host auto-antibodies, nutrients, and peptides affect the circadian rhythm and disrupt the intestinal microbiota. Although FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet and faecal microbiota transplantation have produced successful results in IBD patients in recent years, and many issues have been clarified regarding the effects of changes in intestinal microbiota on the pathogenesis of IBD, there are still many questions that need to be answered in the microbiota-gut-brain axis. Although IBD is not a direct life-threatening disease, the frequency and severity of gastrointestinal symptoms require a differential diagnosis for colorectal cancer and other serious gastrointestinal diseases (Thaiss *et al.,* 2014). The coexistence of anxiety and depression in IBD patients more frequently than in the normal population negatively affects the quality of life. Studies conducted in recent years negatively affect the quality of life of IBD patients in both work and social life (Frändemark *et al.,* 2018). This negative situation places a serious burden on the health expenditures of countries. Although IBD is not a direct mortality and life-threatening disease, it is a disease that should be emphasised in our article due to its differential diagnosis with colorectal cancer, its negative impact on

quality of life, and its negative effects on countries' health budgets (Malan-Müller *et al.,* 2023).

The microbiome and the central nervous system

Intestinal microbiota has an active role in regulating various physiological and physiopathological processes. The maintenance of homeokinesis depends on the interaction between the brain and the stomach, which is two-way (Alagöz, 2017). This interaction is provided by endocrine, immunohumoral connections, and metabolites. Microbial compounds, cytokines released from mucosal cells, afferent neural pathways, such as the vagal nerve, and serotonin released from intestinal cells are a few variables that contribute to brain-gut interaction (Kashtanova *et al.,* 2016). Polyamines, neuropeptide-like substances, neurotransmitters, and neuromodulatory chemicals can all be synthesised by gut bacteria. Firstly, these metabolites and chemicals constitute the brain-gut-microbiota axis and the microbiota–gut interaction area (Donoso *et al.,* 2022).

The second brain is the term used to describe the enteric neural system (ENS) of the gastrointestinal tract. The ENS and the central nervous system (CNS) control intestinal physiology. The vagus nerve, pelvic nerves, and sympathetic pathways serve as interfaces between the ENS and the CNS. In the activity of the stomach, the CNS is involved. By using vagovagal reflexes, it also controls acid secretion and contractile activity (Kashtanova *et al.,* 2016). The small intestine and colon are controlled by the CNS, which also controls other biological functions such as transmucosal fluid flow, local blood circulation, and muscular activity. The ENS is primarily responsible for controlling intestinal motility. In the absence of CNS influence, gastrointestinal processes are maintained, but if control of the enteric nervous system is lost, the life-sustaining force is lost. In the CNS, the vagus nerve in the brainstem, spinal pathways in the thoracolumbar spinal cord, and pelvic nerves in the lumbosacral spinal cord are all associated with the gastrointestinal tract. Vagal afferents carry mechanoreceptive and chemoceptive information from the oesophagus, stomach, and intestines to the CNS but do not transmit pain, whereas thoracolumbar and lumbosacral afferents perceive the pain of intestinal origin. Vagal neurons control gastric motility, acid secretion, and hormone release at synapses in the enteric nervous system. Ultimately, the gastrointestinal tract is controlled by integrated centers in the brainstem, spinal cord, and sympathetic ganglia (Tanaka & Nakayama, 2017). The brain-gut microbiota-CNS axis contains a complicated connection. The decrease in physical health and the emergence of various illnesses are both significantly influenced by disorders in this system. Negative microbiota (dysbiosis) affects the immune function of the brain, the blood–brain barrier, and the connection between the gastrointestinal nerve and the central nervous system (Tanaka & Nakayama, 2017). Attention deficit hyperactivity disorder (ADHD), cognitive development retardation, alterations in fear response, mood changes (depression and anxiety), and autistic spectrum disorder in children can all be caused by dysbiosis (Tanaka & Nakayama, 2017). The microbiota also plays a crucial role in activating the vagus nerve to transfer the information from the gastrointestinal tract to the nucleus tractus solitarius and help coordinate the body's function and regulate them (Han *et al.,* 2022).

The microbiome and the immune system

The immune system recognises and responds to many molecules, helping to differentiate self from non-self. The gut microbiome, which includes the most foreign molecules, thus plays a crucial role in the immune system development of infants (Tanaka & Nakayama, 2017). The body's immune response protects the fetus and infant from the mother at first (Kashtanova *et al.,* 2016). It must be strengthened, infections must be identified, and the body's defence against pathogens must be formed throughout infancy and early childhood (Ficara *et al.,* 2020). It depends on differentiating immune cells from self and non-self and developing secondary immunological organs in infancy and childhood, *viz*., lymph nodes, Peyer's patches, and thymus. Pathogens are recognised by congenital immune cells, which trigger an immunological response (Ficara *et al.,* 2020), and this is essential for maintaining immunological resistance to commensal flora (symbiotic and pathogenic microorganisms) (Kashtanova *et al.,* 2016). The immune system, which grows in tandem with the cell's growth and development, alerts the cells about potential pathogens and programs reactions to defeat them (Tanaka & Nakayama, 2017). It provides numerous stimulation such as Paneth and Goblet cells and cytokines through its connection with the gut, *i.e*., epithelial barrier and epithelial cells (Tanaka & Nakayama, 2017). Understanding the relationship between gut microbiota and the host's immune system is crucial for developing more effective and safe treatment agents against actionable targets. These modulatory interventions have promising activities, including faecal microbiome transplantation (FMT), prebiotics, probiotics, antibiotics, and dietary interventions (Dixit *et al.,* 2021). But the exact role of the gut microbiome in immune response and preservation of the host's health is still unclear.

The microbiome and the lung development

The existence of the gut-lung axis implies that alterations in the gut microbiota are responsible for some lung diseases (Tanaka & Nakayama, 2017). In a study with mice lungs, stimulation of the lungs with

lipopolysaccharide is reported to significantly increase the number of bacteria in the intestinal cecum that can be modulated by antibiotics. In addition, pneumonia induces intestinal damage and reduces intestinal epithelial proliferation. Lung infections can be prevented *via* a process involving the liver and short-chain fatty acids from the gut microbiome (Barcik *et al.,* 2020). Activated immune cells in the gut travel *via* lymph or blood to the lung, where they have effector functions (Tanaka & Nakayama, 2017). The development of intestinal microbiota reduces the risk of many respiratory system diseases, especially asthma (Wang *et al.,* 2021); however, several parameters such as exposure to farm animals, to insects, pests or rodents dust, as well as living in urbanised areas, are responsible for respiratory problems (Tanaka & Nakayama, 2017).

Microbiome and body growth

The gut microbiome influences growth from birth through energy supply and growth hormone stimulation (Tanaka & Nakayama, 2017). The microbiome affects weight gain in infants and children, with conditions such as increased energy accumulation, fat storage, and satiety stimulation (Tanaka & Nakayama, 2017).

The relationship between microbiota and the development of cancer

First reports of the relationship between microorganisms and cancer date back to the nineteenth century, with observations of spontaneous tumour regressions after *Streptococcus pyogenes* infections. Consistent with these findings, recent research showed that the microorganisms within the body, especially those living in the gut, have essential roles in carcinogenesis, immunosurveillance of tumour cells, and response to immunotherapy. It is known that intrinsic microorganisms also have effects maintenance of health. These findings bring about the idea of developing new treatment strategies for cancer targeting the microbiota. One of the most remarkable steps in cancer treatment is the discovery of immunotherapeutic agents. Improvements in the overall survival (OS) of patients with different cancer types have been reported with immune checkpoint inhibitors (ICI) (Rini *et al.,* 2019). But these good responses with ICIs are not seen in all patients because of primary or acquired resistance (Sharma *et al.,* 2017). With this knowledge, it is easy to consider an unmet need for improving treatment strategies for these patients to overcome resistance. Various genomic and molecular biomarkers associated with response to ICIs have been determined (Morad *et al.,* 2021). In line with these data, it is also found that microorganisms living in the flora of the host and the genes of these microorganisms also called the microbiome, have a role in response to ICI. The most crucial component of this microbiome is determined by the microorganisms living in the gut; patients with cancer have different gut microbiomes from healthy individuals; it is considered that the gut microbiome has predictive and prognostic roles in response to ICI (Yonekura *et al.,* 2022). New microbiome-based treatment strategies have been developed in recent years to modulate gut microorganisms to improve the efficacy of ICIs (Baruch *et al.,* 2021a, 2021b) while decreasing the frequency of adverse events (Wang *et al.,* 2021). This section aimed to evaluate the role of microbiota in carcinogenesis and in response to cancer therapies and the manipulation of microbiota to improve outcomes in cancer patients.

Microbiota and carcinogenesis

It is known that the gut microbiome interacts with the host's immune system and affects health and carcinogenesis (Helmink *et al.,* 2019). Recently, the microbiota was defined as an enabling factor of 'Hallmarks of Cancer' (Hanahan, 2022). The association between microbial dysbiosis and chronic inflammation and the role of inflammation in carcinogenesis are well-known situations. The various microorganisms cause this proinflammatory status by producing cytokines. Tissue microbiota can initiate an inflammatory environment by producing toxins that lead to carcinogenesis (Lee *et al.,* 2021). It is not astounding that microorganisms influence cancer development, and this relationship has been shown in gastric cancer and *H. pylori*, colorectal cancer, and *Fusobacterium* (Woo *et al.,* 2022). It was determined that gastric cancer would develop in 2–3% of people with *H. pylori* infection. Additionally, this microorganism is associated with genomic instability and double-strand breaks that cause gastric carcinogenesis (Xie *et al.,* 2020). Besides bacteria, it was reported that fungi have also been associated with developing pancreatic adenocarcinoma (Aykut *et al.,* 2019).

The skin is the largest organ, the most crucial barrier against external threats, and has major immunological roles (Woo *et al.,* 2022). Various studies have reported an association between different microorganisms and cancer types. For example, alterations in the skin microbiota seem to affect the development of non-melanoma skin cancer (Squarzanti *et al.,* 2020). A trial conducted in Taiwan has also reported an increased risk of human papillomavirus infection in patients with non-melanoma skin cancer (Chen *et al.,* 2021). Similarly, Merkel cell polyomavirus has an essential role in the pathogenesis of Merkel cell carcinoma, and its presence is associated with a high tumour burden (Mokánszki *et al.,* 2021). In recent clinical research conducted on patients with acral melanoma, a strong association with *Corynebacterium* presence in skin swabs was found in stage 3–4 compared to stage 1–2 disease (Mizuhashi *et al.,* 2021). A relationship between *Fusobacterium* and oral cancer

development has also been defined (Fujiwara *et al.,* 2020). All these studies support the association between skin microbiota and cancer development. But, contrary to these findings, data shows that different mechanisms associated with the bacterial microbiota affect protection against cancer (Luo *et al.,* 2020). Furthermore, tissue microbiota influences a tumour's immune structure, leading to positive and negative effects on progression (Derosa *et al.,* 2020).

Tumour microenvironment and tumour microbiota

In recent years, besides the gut microbiota, evaluating the intratumoral microbiome and changing its composition to improve treatment response in cancer patients have become a new modality. It is known that the microorganisms in the tumour tissue influence carcinogenesis and response to cancer therapies. Different tumours, including of brain, of lung, of bone, the malignant melanoma, and breast cancer, have specific microbiota in their tumour microenvironment (TME) (Poore *et al.,* 2020). These microorganisms live in the intracellular space of the tumour, stroma, and immune system cells. The tumour microbiota was significantly different between ICI responders and nonresponders in patients with malignant melanoma (Nejman *et al.,* 2020).

TME is usually hypoxic and rich in nutrients, making it an optimal habitat for different facultative or anaerobic bacteria (Heymann *et al.,* 2021). This colonisation paves the way for cancer development and progression, influencing the treatment response and antitumor immunity (He *et al.,* 2021). The metabolites secreted from microorganisms that influence cancer development include DNA damage boost, changes in the immune system, and modulation of available metabolite (González-Sánchez & DeNicola, 2021). Several carcinogenesis mechanisms are driven by tumour microbiota. Tissue microbiota may lead to carcinogenesis by altering the host's genome, such as inducing double-stranded DNA breaks and oxidative stress on DNA (He *et al*., 2019). Some microorganisms lead to genomic instability by influencing DNA mismatch repair (Santos *et al.,* 2017). A disruption in the cellcycle by the viruses may also initiate carcinogenesis. Local epigenetic landscape and hijacking of host transcription are also determined as mechanisms that lead to carcinogenesis. Unfortunately, there are many unclear topics about the exact role of the microbiota in solid malignancies, as some induce tumour growth while others inhibit it. However, research is ongoing, and new strategies targeting the microbiome of malignant tumours (Das *et al.,* 2020; Nejman *et al.,* 2020).

Tumour microbiota provides tumour progression by configuring immune tolerance (Das *et al.,* 2020). It plays a vital role in suppressing the immune system by changes in cytokines in the local TME and altering immune regulator ligands of cancer cells (Kalaora *et al.,* 2021). Contrarily, tumour microbiota supports the immune system against cancer in various circumstances. An inverse correlation between *Faecalibacterium* presence and worse PFS and OS was reported in metastatic malign melanoma patients treated with ipilimumab (Lei *et al.,* 2020). Besides, it was reported that tumour microbiota might behave as a focal target for lymphocyte invasion (Poore *et al.,* 2020). Protein and peptide antigens located on cancer cells stimulate the immune system in TME of head and neck squamous carcinoma and malign melanoma; this stimulus enhances the antitumor activity of immune cells and is associated with improved outcomes (Kalaora *et al.,* 2021). With the recent advances in diagnostic tests, such as next-generation sequencing (NGS), we have more accurate results from analysing microorganisms living in cancer cells. These developments provided data about the distribution and relation of microbiota with health and diseases. However, contamination of the samples during the gathering processes is still a significant problem (Eisenhofer *et al.,* 2019). Nevertheless, targeting tissue-based and tumour-based microbiota after determining the dominant microorganisms is a new area of research.

Microbiota and response to cancer therapies

Previous research investigated gut microbiota and ICI response, which emerges with several mechanisms, such as the interaction between the microorganisms living in the gut that changes the ecosystem (Derosa *et al.,* 2021). The microorganisms also affect the enterocytes and lymphoid tissue of the intestines, and the stimulation of various receptors leads them to perceive adjuvant signals. Another mechanism is the secretion of hormones from the gut that have systemic neuroendocrine effects (Yoon *et al.,* 2021). Polyamine and vitamin B production have systemic metabolic effects, and lastly, the stimulation of immune responses against the antigens of microorganisms is cross-reactive against the tumour-associated antigens (Grajeda-Iglesias *et al.,* 2021). All of these factors influence cancer treatments *via* patient-specific and tumour-specific features. It was reported that broad-spectrum antibiotics reduced the gut's bacterial diversity, which harmed the response to ICI. Research reported in recent trials that progression-free survival (PFS) and OS of cancer patients treated with broad-spectrum antibiotics shortly before or during ICI treatment is shorter than those who did not (Khan *et al.,* 2021). It is mentioned that a miscellaneous and untouched microbiota would provide better responses to ICI for cancer patients, whereas a flora distortion might lead to worse outcomes (Derosa *et al.,* 2021). Earlier findings supported a difference between the patients with or without cancer in terms of the dominance of a particular microorganism in the gut flora. Furthermore, it was reported that various

microorganisms were related to ICI response in several cancers (Derosa *et al.,* 2022).

The signature of the gut microbiota is related to the toxicity of cancer therapies and treatment response (Cascone *et al.,* 2021). Thus, several methods were developed to reduce the frequency of toxicities due to treatments, such as FMT and targeted microbial-modulating therapy. The benefit of FMT, indole 3-propionic acid, and *Bifidobacterium* administration has been shown in different cancer types and treatments. It was reported that viruses, bacteriophages, and fungi might have a role in treatment response and toxicity similar to bacteria. The major barrier to determining these microorganisms' role is the lack of knowledge about proper sample preparation, sequencing, data processing, data analysis, and evaluation methods (Vemuri *et al.,* 2020; Liu *et al.,* 2021). Considering these findings in planning future studies was recommended.

Autophagy

Impaired autophagy plays an essential role in the pathogenesis of various cancer types and affects the survival and death of tumour cells. There is a close relationship between the microbiota and autophagy that activates the immune system. Although the exact correlation is still unclear, a relationship between autophagy and cancer was reported (Li *et al.,* 2020). The crosstalk between the microorganisms and autophagy also affects cancer progression (Wang *et al.,* 2021). It has been reported that *F. nucleatum* is associated with resistance to chemotherapy agents such as 5-fluorouracil and docetaxel *via* autophagosomes (Liu *et al.,* 2021).

Similarly, colorectal cancer chemotherapy resistance was observed with autophagosome formation (Hu *et al.,* 2021). An association between the proliferation and invasion of colon cancer cells and *H. pylori* infection-induced autophagy has been defined (Zhong *et al.,* 2021). It has been shown that chloroquine, an antimalarial agent (Martinez *et al.,* 2020), enhanced the antitumor activity of gemcitabine in gall bladder cancer *via* inhibition of autophagy (Wang *et al.,* 2020). Although these findings make chloroquine a good candidate for the future treatment of cancer patients, its toxicity should be considered (Lebin & LeSaint, 2020). Similar results were observed with itraconazole which decreased colon cancer cell proliferation by inducing autophagy and apoptosis (Deng *et al.,* 2020). In line with these findings, modulation of the relation between the microbiota and autophagy may enhance the efficacy of cancer treatments and improve outcomes.

The role of fasting on the microbiota

There are reports about the relationship between fasting and changes in the microbiota. In a study, it is reported that intermittent fasting affects the composition of the gut microbiome. The authors also mentioned that this change leads to altered function of microbiota and its interaction with the host. Similarly, the authors of some other studies reported that fasting and feeding habits have significant effects on the gut microbiota (Thaiss *et al.,* 2014). In a trial, researchers observed that every other day fasting re-shaped the gut microbiota, which led to an increase in the beiging of adipose tissue in mice (Li *et al.,* 2017). It is obvious that there is an urgent need to identify the relationship between fasting and alteration in microbiota in humans.

Nutrient role in microbiota

Diet is one of the essential factors in shaping intestinal microbiota. Dietary macro and micronutrients can modulate gut microbiota composition and metabolic activity, resulting in a range of positive or negative effects on health (Ramos & Martín, 2021). According to the food consumed in the diet (macronutrients, micronutrients, bioactive compounds, *etc.*), there is an increase in the colonisation of selected bacterial species in the microbiota. In a human study, increased colonisation of bacteria was observed in the intestinal microbiota of the group with high animal-based protein, *Alistipes putredinis*, *Bilophila wadsworthia,* and *Bacteroides* sp. In the intestinal microbiota of the group that received high plant-based protein, it was observed that bacterial species of the genus saccharolytic *Prevotella*, *Roseburia*, *Eubacterium rectale*, *Faecalibacterium prausnitzii* increased (David *et al.,* 2014). Since different bacteria ferment each food component, an increase in bacterial colonisation using that food type occurs, and the dominant bacterial species can be shaped according to the diet (Smith *et al.,* 2022). Dietary changes in the microbiota, depending on the type and duration of nutrition applied, it may have positive or negative effects on host health.

Several micronutrients (polyphenols, vitamins, minerals, and trace elements) and macronutrients (carbohydrates, fats, and protein) show effective properties in modulating the microbiota, as shown in Fig. 2. The inappropriate intake of nutrients is responsible for lowering gut microbiota diversity (Yang *et al.,* 2020). The microbiota absorbs the nutrients from the food, which used the break down complex molecules into simpler compounds. Fruits, vegetables, tea, wine, and coffee are the excellent source of polyphenols such as stilbenes, phenolic acid, lignans, and flavonoids which show a higher potential to regulate the microbiota by controlling the oxidative, carcinogenic, and inflammatory activities, inhibiting the growth of *Staphylococcus* sp. and *Helicobacter pylori* harmful pathogens. The microbiota synthesises Vitamins K and B, a natural compound. Similarly, the mineral and trace elements effectively interact with gut microbiota. The changes in gut microbiota, when linked with lean phenotype, are

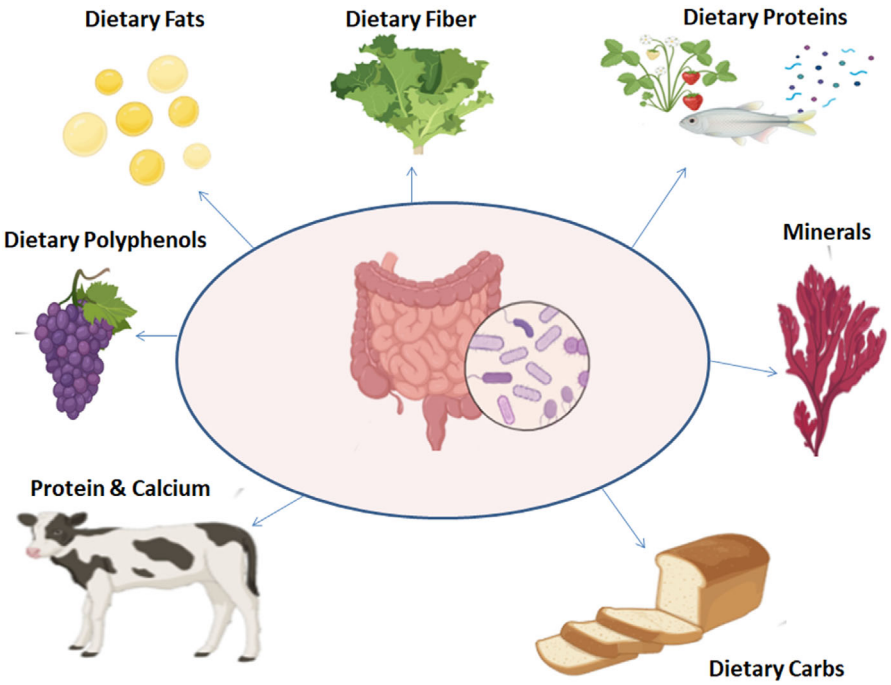

Figure 2 Represent the role of nutrients in gut microbiota health.

controlled by the intake of a higher amount of calcium (Huda *et al.,* 2019). The gut microbiota can produce vitamin B6, which works as a cofactor in different biological reactions directly linked with the immune response as a host. The appropriate level of vitamin B6 helps enhance microbiota activity with the association of lymphoid organs. The microbiota will modulate at different parameters such as F/B ratio and genus level by intake of carbohydrates (Yang *et al.,* 2020). The additional carbohydrate prebiotics such as -arabinoxylan-oligosaccharides, arabinoxylans, and xylooligosaccharides help enhance microbiota activity. At the same time, arabinoxylan-oligosaccharides help to stimulate the specific colon bacteria activity and break down the compounds in the colon. Arabinoxylans target physiological processes and increase health benefits. However, xylooligosaccharides help to maintain the microbiota and target the bifidobacterial population to grow, reducing the cause of inflammation diseases. The protein intake substantially affects microbiota activity like growth factors and reduces the level of anaerobic bacterium like *Clostridium*. Arabinoxylan (AXE), resistant starch (RS), oligosaccharides, inulin type fructan, and galacto-oligosaccharides (GOS) increase the activity of gut microbes, show highly bifidogenic effects, and increase the level of *Roseburia*, *Bifidobacterium*, *Bacteroides*, *Ruminococcus,* and *Lactobacillus* which directly linked with various health benefits (Yang *et al.,* 2020). A study has done to see the effect of nutrients on microbiota activity. In the study, it was observed during overweight menthe F/B ratio increased due to the intake of resveratrol and epigallocatechin-3-gallate, which enhance the activity of gut microbiota (Most *et al.,* 2017). In intestinal microbiota, other study revealed that polyphenol intake influences the body mass index and gender, but the specific mechanism behind the gender difference is unclear. In another finding, it was observed that polyphenols are responsible for increasing the level of Bacteroides individually in the microbiota metabolism (Mayta-Apaza *et al.,* 2018). The report of Cluny *et al.* (2015) revealed that a six-week study occurred on obese rats to observe the effect of carbohydrates on the microbiota. As a result, 10% oligofructose in the diet of obese rats shows an elevation in *Clostridium leptum* and increases the level of *Roseburia* sp., *Lactobacillus* sp., and *Bifidobacterium* sp. Another study occurred on a mice model where the high-fed diet was induced with mung bean protein and observed the level of bile acid is influenced in the *Ruminococcacea* family members, which helps to enhance health (Nakatani *et al.,* 2018).

Dietary carbs and microbiota

With bacterial fermentation of carbohydrates that can reach the microbiota without being digested, short-chain fatty acids (SCFA), the energy source for colonocytes, are formed (Gentile & Weir, 2018). SCFA

suppresses food intake by activating vagal afferents and is thought to affect hunger and satiety signals. While an increase in plant-based fibre intake does not increase intestinal microbiota diversity, it improves microbiota function by causing an increase in short-chain fatty acid production (Wastyk *et al.,* 2021). Although it varies depending on the amount and type of dietary fibre, the most produced SCFAs are; acetate, propionate, and butyrate (Thomas & Denu, 2021). Butyrate, one of the SCFAs, has an anticarcinogenic effect by increasing colon cancer cell apoptosis and an anti-inflammatory effect in the colon epithelium (Gill *et al.,* 2018). With a diet rich in arabinoxylan, an increase in plasma SCFA rates and an improvement in glucose tolerance were observed (Goswami *et al.,* 2018). In the coming years, interventions to increase SCFA production in the intestinal tract may be considered due to its potential impact on the prevention or treatment of various types of cancer (Mirzaei *et al.,* 2021). A high-fat and high-sugar Western diet contains a lower amount of dietary fibre and indigestible polysaccharides, which are microbiota-accessible carbohydrates. In diet model with a lower amount of carbohydrates can access the microbiota, which shows several consequences that threaten host health, which may cause a weakening of immunity by disrupting intestinal homeostasis, an increase in the risk of infection and autoimmune disease development (Daïen *et al.,* 2017).

Dietary proteins and microbiota

Dietary proteins cause changes in microbiota composition, depending on the protein source, resulting from proteolytic fermentation in the colon. Due to plant-based protein fermentation and increased SCFA (acetate, propionate, and butyrate) production, the intestinal barrier is strengthened, and inflammation is reduced (Duncan *et al.,* 2021). As a result of animal protein fermentation, butyrate production decreases while amino acid-derived SCFA production increases (Gilbert *et al.,* 2018). In addition, a large cohort study found that increased intake of animal-based fat due to high animal-based diet consumption increased the risk of colon cancer.

Dietary fats and microbiota

High-fat diet; may initiate inflammation by causing an increase in intestinal permeability, pro-inflammatory cytokine release, and endotoxin levels (Ye *et al.,* 2021). On the other hand, systemic inflammation has been associated with an increased risk of cardiovascular disease, diabetes, and various types of cancer. Animal studies have shown that a high-fat diet alters microbiota diversity and its function in the host. The type of fat is as essential as the amount of dietary fat in the homeostasis of the microbiota. While a diet with a high saturated fat content causes a decrease in the diversity and richness of the microbiota, diets rich in polyunsaturated fatty acids increase the diversity of the microbiota (Mokkala *et al.,* 2020; Yoo *et al.,* 2021).

Dietary polyphenols and microbiota

Polyphenols in plant-based foods are nutraceutical agents with antioxidant, antidiabetic, anticancer, and anti-inflammatory properties. A diet rich in polyphenols and protective against cancer supports immune function by increasing host–microbiota interaction (Mileo *et al.,* 2019). While 5–10% of the polyphenols are absorbed from the small intestines and enter the systemic circulation, 90–95% reach the colon without being absorbed. Lignans, among the polyphenols used in treating inflammation, have a wide variety of plant sources, such as flaxseed, sesame seeds, legumes, whole grains, vegetables, and fruits. Polyphenols, which undergo enzymatic reactions by bacteria in the colon, turn into metabolites that provide physiological benefits. Polyphenols that reach the colon without being absorbed can have a prebiotic effect and may contribute to the modulation of intestinal microbiota by causing a decrease in the number of pathogenic bacteria and increasing the number of beneficial bacteria (Ma & Chen, 2020). The anticancer effect of lignans occurs through the regulation of gene expression associated with cancer development. Lignans in flaxseed are metabolised by Ruminococcus bacteria in the intestinal microbiota and converted into enterolignans, including enterodiol and enterolactone, which have been associated with anticancer activity. The health benefit of dietary polyphenols depends on the microbiota's metabolic activity, whereas the intestinal microbiota's role is essential (Taibi *et al.,* 2021).

Fermented foods and microbiota

In the literature, human studies show that consuming fermented foods such as kefir, yogurt, and kimchi is protective against proinflammatory processes that result from intestinal dysbiosis (Stiemsma *et al.,* 2020). It has been shown that an increase in fermented food consumption improves the immune response by causing an increase in microbiota diversity and a decrease in inflammatory markers. A study by Wastyk *et al.* (2021) emphasised that the rise in fermented food consumption might be necessary for decreasing intestinal microbial diversity and reducing inflammation in industrialised societies. Many studies have observed that the risk of autoimmune diseases such as type 2 diabetes and cardiovascular diseases decreases with an

increase in fermented food consumption (Qu *et al.,* 2020).

New strategies targeting the microbiota

As the microorganisms living in the gut and the tumour itself play essential roles in immune response, it would not be a mistake to think that manipulating the microbiota with various interventions might lead to enhanced antitumor activity and increased treatment efficacy. These interventions include FMT, targeting microbial environment, altering diet habits, using prebiotic and probiotic products, administering antibiotics, and phage-based methods (McQuade *et al.,* 2019). These strategies have been evaluated in various studies that included cancer patients and are also under evaluation in ongoing clinical trials.

FMT is the most drastic yet effective strategy for manipulating gut microbiota. During the procedure, the entire gut microbiota of a donor, generally a healthy individual or a patient with cancer with a good treatment response, is transplanted into a recipient. The efficacy of FMT in reversing ICI resistance and improved responses were shown in malign melanoma patients. Increased immune cell infiltration in the tumour and gut of these patients were reported, and enriched serum metabolites specific to treatments were determined (Baruch *et al.,* 2021a, 2021b). The study said affords were canalised to select the ideal donor candidate for FMT in cancer patients, whether a patient with complete response to ICI or a healthy individual. Promising findings in cancer patients were reported with a combined approach of ICI treatment and FMT from donors with a complete response or healthy individuals (Maleki *et al.,* 2020). However, the difficulties in FMT research, including determining ideal donors, the definition of optimal preparative treatments for FMT, and the administration route, should be considered (McQuade *et al.,* 2019).

After trials that showed the benefit of FMT in cancer treatment, researchers are focused on new approaches to the modulation of gut microbiota. One of these strategies is to transplant only one specific species instead of transplanting the whole gut microbiota of a donor. Improved outcomes were reported in patients with metastatic renal cell carcinoma treated with a bacteria formulation added to ICI (Dizman *et al.,* 2022). Similar findings were observed in various trials evaluating the transplantation of different bacteria species to cancer patients receiving ICI (Lauté-Caly *et al.,* 2019). Inhibition in tumour growth was observed with probiotic-derived ferrichrome (Kita *et al.,* 2020). On the other hand, it is too early to say which is the best strategy for treating a cancer patient. Early promising results were determined with DTA81, an oral probiotic candidate, in preventing colorectal cancer development (da Silva Duarte *et al.,* 2020). Contrary to these good responses, some trials reported worse outcomes with the addition of probiotics to ICI therapies in cancer patients (Derosa *et al.,* 2020). However, recent research reported ICI responses, including patients with different cancer types with specific gut microbiota (Cabrita *et al.,* 2020). Although worse responses to ICI treatments in cancer patients were reported with broad-spectrum antibiotics that disrupt the gut microbiota (Wilson *et al.,* 2020), killing pathogen microorganisms with specific antibiotics may lead to expansion of beneficial microbiota, and this might result in improved treatment responses (Selle *et al.,* 2020). Besides direct interventions to the gut microbiota, changing dietary habits influences the composition of gut microbiota. The dietary strategies that might be beneficial when administered with immunotherapies include short-term starvation, a diet with high fibre content, restriction of calorie intake for an extended period, taking oral micronutrients, and a ketogenic diet (Wang *et al.,* 2021). There are ongoing trials combining dietary recommendations with interventions that aim to modulate the gut microbiota of cancer patients receiving anticancer therapies (Baruch *et al.,* 2021a, 2021b). It was reported that high fibre intake with diet is associated with improved outcomes in cancer patients treated with ICI. Chemically defined and non-digestible fibres, prebiotics can modulate the gut microbiota as diet does (Becerril-Alarcón *et al.,* 2019). But it should not be forgotten that the effects of prebiotics depend on the microorganism populations of the gut microbiota. Besides, the assessment of immune cells present in the body and TME will provide to develop strategies to target these immune mechanisms, which may lead to discovering new approaches to prevent and treat cancer (Mao *et al.,* 2021). Many emerging technologies are still being developed, including metabolomic profiling, wearable devices, ingestible mini-capsules, smart toilets, and artificial models. Different approaches will be chosen for the patients with a markedly dysbiotic profile (determined as low diversity and an abundance of unfavourable or pathogenic microbiota leading to impaired functional status), moderately dysbiotic profile (defined as intermediate diversity and consisting of some favourable microorganisms with relatively preserved functional status), and favourable profile (Park *et al.,* 2022). All these strategies mentioned above will provide a more optimised personalised cancer treatment and improved health (Smith & Jheeta, 2020; Smith *et al.,* 2022).

Future perspective

Timeously, microbiota plays a crucial role in the human body for the development of several functions in appropriate ways and prevent different life-threatening diseases by targeting them. It is the complex ecosystem in the human body that initiates the functioning from birth

the whole life. In future work on more new techniques, such as diagnostic and prognostic tools, radio frequency identification, real-time detection, and biomarkers, was used to identify and solve the problem caused by the improper microbiota (Cullen *et al.,* 2020). The review provides information about the microbiota, how it targets promising diseases and cures them, and the role of nutrition in the body to develop healthy microbiota. Although there are available data on different tools and biomarkers to cure and maintain healthy microbiota, more research is required to understand the mechanism of gut microbiota.

Conclusion

In line with the findings from previous clinical trials, the microbiota has a vital role in disease occurrence and health maintenance. Thus, determining the microorganisms in different host tissues will contribute to precision cancer care and health. Histopathologic, genomic, and proteomic evaluation of tumour tissue constitutes the main point of personalised cancer care. It is thought that profiling the microbiota of the host and the tumour tissue will be one of the most important topics of clinical trials. With a better understanding of microbiota's role in maintaining health and developing diseases, new treatment strategies targeting these microorganisms to modulate the microbiota have emerged in recent years. There is a long way to go to determine which microorganisms affect physiological and pathological events and the proper interventions to modulate the microbiota in cancer treatment. But it is thought that modulating the microbiota with various interventions added to cancer therapies would be an indispensable leg of precision oncology in the coming decade. Nutrition shows the major role in maintaining gut microbiota health by showing protective properties against harmful diseases. Nowadays, food products such as fermented dairy foods, fruits, and vegetables, nutraceutical products, *etc*., are more in intensive research due to their most developed functional properties.

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Author contributions

Emel Oz: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Aysegul Simsek:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Melih Simsek:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Nihal Tuncer:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Muharrem Bayrak:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Kenan Çadırcı:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Charles Brennan:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Mukul Kumar:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Charalampos Proestos:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Margaret Brennan:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Tahra Elobeid:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Maomao Zeng:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Igor Tomasevic:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Elif Ekiz:** Investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Fatih Öz:** Conceptualization (equal); investigation (equal); resources (equal); supervision (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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References

This article is important for our manuscript. Because we have generally benefited from this article when describing the relationship between microbiota and human health.

This article is important for our manuscript. Because we generally benefited from this article while describing the relationship between microbiota and healthy life.

This article is important for our work. Because we generally benefited from this article when compiling information about the gut microbiota.

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