REVIEW ARTICLE

Microbiota's role in health and diseases

Amr El-Sayed[1] · Lotfi Aleya[2] · Mohamed Kamel[1]

Abstract

The microbiome is a term that usually refers to the community of various microorganisms that inhabit/live inside human/animal bodies or on their skin. It forms a complex ecosystem that includes trillions of commensals, symbiotics, and even pathogenic microorganisms. The external environment, diet, and lifestyle are the major determinants influencing the microbiome's composition and vitality. Recent studies have indicated the tremendous influence of the microbiome on health and disease. Their number, constitution, variation, and viability are dynamic. All these elements are responsible for the induction, development, and treatment of many health disorders. Serious diseases such as cancer, metabolic disorders, cardiovascular diseases, and even psychological disorders such as schizophrenia are influenced directly or indirectly by microbiota. In addition, in the last few weeks, accumulating data about the link between COVID-19 and the microbiota were published. In the present work, the role of the microbiome in health and disease is discussed. A deep understanding of the exact role of microbiota in disease induction enables the prevention of diseases and the development of new therapeutic concepts for most diseases through the correction of diet and lifestyle. The present review brings together evidence from the most recent works and discusses suggested nutraceutical approaches for the management of COVID-19 pandemic.

Keywords Bacteriophages · COVID-19 · Microbiota · Virome · Virobiota · Microbiome · Health

Introduction

The microbiome consists of various bacteria, archaea, fungi, protozoa, and even viruses. A*t least 800 different bacterial species could be isolated* from healthy humans' gut (MUNIESA AND JOFRE 2014; EL-SAYED ET AL. 2021). In addition, members of the viral pool inhabitant in the gut (virome) have been recently identified in the gut. The virome consists mainly of bacteriophages, plant-derived viruses, and various giant viruses. In contrast to the gut's bacterial inhabitants, most of the virome members have not been previously recognized due to technical difficulties in the detection, identification, and isolation of the saprophytic gut viruses. On average, one gram of stool is estimated to contain at least 10^9 virus-like particles (VLPs) and 10^9 bacterial cells (Kim et al. 2011). However, the microbiota composition is dynamic and undergoes continuous changes in response to external factors, including nutritional status, environmental factors, lifestyle, health status, and diseases, medications such as antibiotics (Table 2) (Scarpellini et al. 2015; El-Sayed et al. 2021). For example, the administration of high doses of antibiotics for 3 weeks leads to a dramatic reduction in the amounts of gut microbiome and fecal DNA content (Pak et al. 2019). The impact of infectious diseases and different strategies for their treatment and control on microbial dysbiosis are illustrated in Figure 1.

The influence of microbiota on our health and disease status is exerted in many directions. They can induce/modify metabolic-, auto-immunogenic, and neurodegenerative diseases. In addition, they regulate the host immune response and modulate drug interactions (Grice and Segre 2012). Their effect on our health can only be understood if we know that human origin cells constitute only 10% of the total number of living cells in human bodies. In comparison, the microbiota represents the remaining 90% of the cells. Similarly, only 1% of the total unique genes in our bodies have a human origin, and the remaining 99% belong to the gut and the oral cavity's microbiota. Therefore, the human microbiome is

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Fig. 1 The impact of microbial pathogens and their strategic treatment on microbial dysbiosis and their outcome in the human host
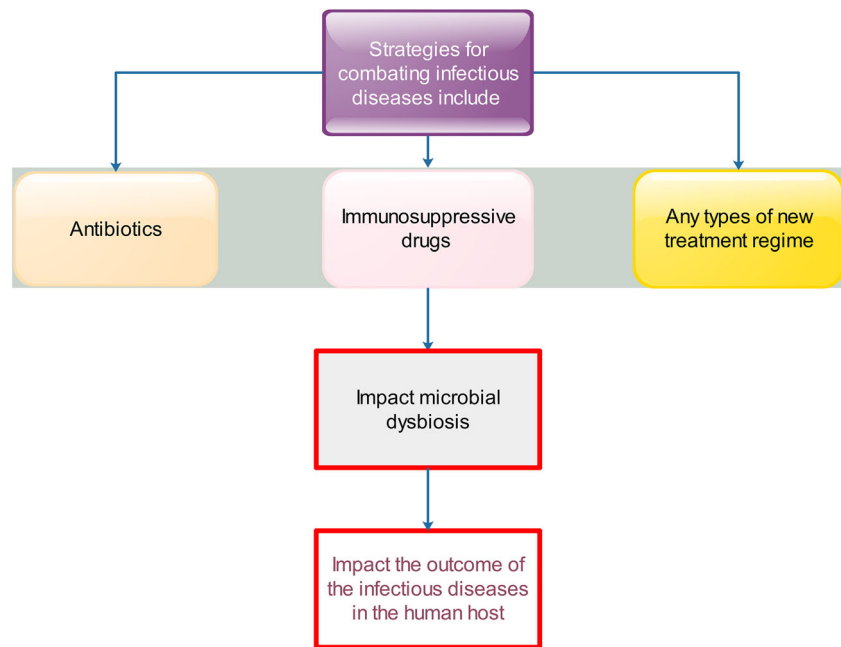
considered our second genome (Tremlett et al. 2017; Scarpellini et al. 2015; Grice and Segre 2012).

Beside the gut, the microbiota can also colonize the oral cavity, nares, vagina, breast, and the skin (Table 1). The oral microbiota consists mainly of streptococci and to a lesser extent other species as *Veillonella, Gamella, Rothia, Fusobacterium*, and *Neisseria*. Although the oral microbiota is essential for the maintenance of oral health, they may induce various diseases such as caries (by *Streptococcus mutans, Veillonella, Lactobacillus, Bifidobacterium*, and *Propionibacterium)* and periodontitis (by *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Treponema denticola*, and *Tannerella forsythia)* (Bik et al. 2010; Aas et al. 2008; Belda-Ferre et al. 2011).

Beside the previously listed bacterial species, viruses (particularly bacteriophages) are also represented in the community of oral microbiota (known as salivary viromes) and may also play a significant role in the induction of oral diseases (Pride et al. 2012). It is worth mentioning that the oral microbiota's harmful effect extends beyond the induction of dental diseases to induce systemic diseases. One of the best examples is the connection between periodontitis and the induction of diabetes and cardiovascular diseases (e.g., atherosclerosis and stroke) where the cholesterol portion narrowing the arteriosclerotic artery walls is synthesized by oral microbiota and does not have a dietary origin as believed (Koren et al. 2011; Leishman et al. 2010; Patrakka et al. 2019).

Competition among different bacterial species has been traditionally used to counteract the harmful effects of invading pathogens. This therapeutic approach is mostly applied for the treatment of gastrointestinal diseases, such as the use of *Saccharomyces boulardii* for the treatment of post-antibiotic

Table 1 Factors affecting the composition of the microbiota

Factors affecting the composition of the microbiota						
Nutritional habits	Environmental	inherited	Lifestyle	Antibiotics	Modulation of gut microbiota	Infections
- During pregnancy - After birth	Such as the way of birth (caesarean or natural birth)	Mainly inherited epigenetic factors from both parents	Including smoking, alcohol consume and sport	A two-edged weapon	Prebiotics, probiotics, and FMT	Not just microbiota affects viral and bacterial infections but vice versa occurs as well
Mainly the consumption of red meat, fibers, and the good and bad fats/oils	As the engulfment of vaginal microflora by the foetus enriches the gut microbiome of the newborn	Due to nutritional and environmental factors which modulate the parent epigenome	e.g., westernized lifestyle versus the live style in developing countries			

diarrhoea (Dinleyici et al. 2012), *Lactobacillus* GG for the treatment of diarrhoea caused by salmonella (Aggarwal et al. 2014), *Weissella cibaria* JW15 (JW15) to inhibit pathogens like *Listeria monocytogenes*, *Salmonella Typhimurium*, *S. enteritidis*, and *Escherichia coli* (Yu et al. 2019). The *E. coli* strain A0 34/86 can also be used to prevent the colonization of pathogenic *E. coli* in the gut of infants (Micenková et al. 2019), while *Escherichia coli Nissle* 1917 is administrated for the treatment of leaky gut (Ukena et al. 2007). Similarly, bacteriophages have been also used to treat antibiotic-resistant MRSA strains (Botka et al. 2019) and infections caused by *Mycobacterium abscessus* (Dedrick et al. 2019). Recently, genetically modified bacteriophages were used for the treatment of pathogens in the gut, even intracellular pathogens (Møller-Olsen et al. 2018).

Alteration in gut microbiota with aging

The microbial content of the GIT tract of infants has a simple structured composition dominated by bifidobacteria. The composition and the prevalence of various bacterial species are influenced by many factors such as the maternal feed during pregnancy, the mode of delivery (normal birth vs. caesarean sections), and the type of feeding (breastfeeding vs. milk replacers). However, the composition of the microbiome changes continuously with age. Comparison of the microbiome composition in infants and in 4-year-old children revealed the reduction in the population of phyla Proteobacteria and Actinobacteria accompanied by the increase in phyla Firmicutes and Bacteroidetes in the gut of the older children (Guo et al. 2020).

In general, as the microbiome functionality differs between infants and adults, therefore the microbial profiles are adapted in response, e.g., while the microbiota involved in amino acid and vitamin metabolism dominates in infants gut, these microbes will be slowly replaced by microbiota participated in fat metabolism with age (Guo et al. 2020).

The microbial structure varies even among elderly populations from different countries in response to age, diet, lifestyle, metabolic diseases like obesity, and environmental influencing factors (Claesson et al. 2011). Therefore, with age, the population of disease-associated pathobionts and facultative anaerobes (Clostridia *and Bacteroides*, Betaproteobacteria, and Deltaproteobacteria) generally increase in conjunction with the reduction of the number of beneficial commensal bacteria (as Actinobacteria, bifidobacterial, *Firmicutes,* lactobacilli, and bifidobacterial), leading to the disturbance of the *Bacteroidetes*:*Firmicutes* ratio (Woodmansey 2007; Pellanda et al. 2021; Odamaki et al. 2016). Although the core microbial profile of elderly persons is clearly distinct from that for younger adults, there is no fixed universal composition of microbiota in the elderly population (Mueller et al. 2006).

These changes share to a great extent in age-related physio-pathological changes leading to inflammaging (gut inflammatory status, usually mediated by NF-κB transcription factor which induces a state of persistent activation of gut innate immunity) in addition to the reduction of both gut immune response and gut epithelial barrier functionality (Walton et al. 2020; Claesson et al. 2011). The alteration in gut microbiome composition and the resulting physio-pathological changes with age were proposed as possible explanations for the difference in COVID-19 susceptibility between young and elderly populations (Zimmermann and Curtis 2020).

Differences in existing microbiota at the geographical level

The composition of microbiota was also found to be influenced by the geographic location due to the differences in environmental (e.g., environmental temperature and water resources) and cultural factors (e.g., type and availability of diet, sport, lifestyle, and stress) (Redondo-Useros et al. 2020; Mohr et al. 2020).

The effect of the culture is clearly seen when comparing the Mediterranean versus Western diet. Evidence linking consumption of the Mediterranean diet and the modulation of the gut microbiome are accumulating. This modulation includes the increase in the population of Lachnospira and Prevotella and the reduction of the population of *Ruminococcus*, which reflects positively on the health status. The protective role of the Mediterranean dietary pattern against diabetes, cardiovascular disease, Crohn's disease, and cancer was reported (Shively et al. 2018).

The shift to Mediterranean diet plan reduces insulin resistance and protects against diabetes by restoring the normal population of *P. distasonis*, *B. thetaiotaomicron*, *F. prausnitzii*, *B. adolescentis*, *Butyricimonas*, *Desulfovibrio*, *Oscillospira*, *and B. longum* (Jin et al. 2019). Similarly, the profiles of gut microbiome varied clearly between African and European children. In African kids, the intestinal flora is more variable, had more Prevotella than *Bacteroides*, and produced more butyrate. This is mainly attributed to the high-fiber low-protein diet consumption in African countries (de Filippo et al. 2010; Yatsunenko et al. 2012; Lin et al. 2013). A direct effect of climatic temperature on microbiota was documented. In high/cold geographical locations, the participation of two phyla changes in response to external temperature. While the prevalence of Firmicutes increases with latitude, the Bacteroidetes population sinks with the latitude. Both phyla are essential for increasing the body mass index and body fats (Suzuki and Worobey 2014).

Other environmental factors like floods and drinking water sources influence the gut microbiome, especially in warm

countries where water-borne pathogens (as salmonella and *E. coli* infections) are common (Yusof et al. 2017).

Distribution of microbiota

The microbiota is present wherever contact with the external non-sterile environment exists. Therefore, they harbor the gut, oral cavity, nares, vagina, and the outer skin layer. Each location has its characteristic inhabitants. Naturally born babies acquire additional bacterial species during their passage via the vagina, mainly *Lactobacillus* and *Prevotella*. In opposite, babies born via caesarean section gain bacterial species similar to those living on the skin, such as *Propionibacterium, Staphylococcus*, and *Corynebacterium (*Dominguez-Bello et al. 2010*)*. Similarly, differences were also found in microbiota's composition the gut of naturally breastfed babies vs. formula-fed (Penders et al. 2006*)*. In addition to the vagina, many studies have been carried out to investigate the presence/absence of bacteria in the gravid uterus. Most of the investigated samples harbored bacterial DNA in the amniotic fluid samples. All mothers and feti involved in these studies were healthy and did not show any signs of infection. The studies referred to the important role of the fatal microbiome for intrauterine development in the immune system (Stinson et al. 2019) (Table 2).

The presence of gut virome was always overseen in human fluid samples as the samples are mostly cultured on bacteriological culture media or tested with PCR using specific bacterial 16S RNA gene probes (Garrido-Cardenas and Manzano-Agugliaro 2017*)*. However, in opposite to the bacterial members of the microbiota, viruses present in the virome (especially bacteriophages) can normally pass through the intestinal wall, circulate in the blood at high concentrations, and cross the physiological barriers as the placenta and the blood-brain barrier (BBB). They, therefore, could be isolated from the cerebrospinal fluid (CSF), which is always thought to be sterile (Tetz and Tetz 2018; Srivastava et al. 2019; Srivastava

et al. 2004). It was estimated that daily, on average, about 31 billion bacteriophages can be transcytosed across the gut epithelium in the human body and spread via blood and lymph to all body organs, including the brain (Nguyen et al. 2017).

Clinical potential of understanding the role of microbiota in disease induction

The changes in the structure and composition of the microbiome have a great influence on the individuum's health and disease status. Understanding the microbiota-gut-liver-brain axis provides a better understanding of microbiota's role in the induction of serious infectious (e.g., COVID-19 and neoplasm) and non-infectious diseases (e.g., diabetes and CNS disorders). Such data are important for (1) the prevention and control of the diseases, (2) for the development of non-pharmaceutical therapeutic approaches (e.g., via probiotics and nutraceuticals), and (3) as disease markers for the early prediction of diseases via monitoring the changes in microbial composition in the gut (e.g., prediction of metabolic diseases) (Ding et al. 2020).

Role of gut microbiota in disease induction

The intestinal mucosal barrier is one of the major body defense barriers, consisting of physical, chemical, microbial, and immunological components. It protects the body against bacterial invasion, the passage of foreign antigens and toxins to the circulation, and against the loss of water and nutrients. It regulates molecular exchange and the coexistence/colonization of gut microbiota. Therefore, the disruption of this balanced equilibrium or the occurrence of leaky gut has serious consequences (Bischoff et al. 2014). The intestinal barrier functionality is supported by the administration of probiotics such as *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Escherichia coli* Nissle 1917, which not only improves the efficiency of the intestinal barrier but also prevents invasion of gut pathogens (*Ukena et al.

Table 2 Different classification of microbiome: the microbiome can be classified according to their type, distribution, and their effect on the animal/human health.

Classification of microbiota according to:		
Type	Distribution	Role
1. Bacteria	• External microbiota (on the outer skin)	a.1. Beneficial microbiota
2. Archaea	• Internal microbiota	(e.g., SCFA and vitamin producing bacteria/probiotics)
3. Fungi	➢ Gut microbiota	2. Pathogenic microbiota
4. Protozoa	➢ Oral microbiota	(e.g., cancer and metabolic syndrome inducing bacteria)
5. Viruses (virome)	➢ Naris microbiota	
➢ Plant-derived viruses	➢ Vaginal microbiota	
➢ Giant viruses	➢ Milk microbiota	
➢ Bacteriophages		

2007*)*. Even minimal changes in gut microbiota composition have great consequences and influence the future development of serious diseases such as neoplasms (Bongers et al. 2014) as shown in Fig. 2.

Coronavirus infection (COVID-19)

Recently, the presence of a strong gut-lung axis was suggested by many authors. This was confirmed during the present COVID-19 pandemic where a clear correlation between infection with COVID-19 and the alteration in the composition of fecal microbiome could be reported. Based on that, modulation of the gut microbiome showed significant alleviation of the symptoms. According to Tursi and his team (2020), the administration of oral probiotic formulation of *Streptococcus thermophilus*, *L. acidophilus*, *L. helveticus*, *L. paracasei*, *L. plantarum*, *L. brevis*, and *B. lactis* could relieve the COVID-19-induced diarrhoea and the risk of respiratory failure and decreases the mortality rates in COVID-19-hospitalized patients (Tursi and Papa 2020; Janda et al. 2020). These effects are attributed mainly to the direct modulatory effect of diet on gut microbiota or through the alleviation of chronic gut inflammation which result from prolonged consumption of red meat and alcohol (Rishi et al. 2020; Ferreira et al. 2020).

Moreover, the gut microbiota was observed to upregulate the production of ACE2 in the gut of laboratory animals. By so doing, the microbiota can influence the ability of the virus to invade the gut epithelium (Walton et al. 2020). The effect of diet on gut microbiota and the prevalence of COVID-19 were clearly noticed during the lockdown, where healthy home-cooked food partially replaced fast food. The accumulating evidence surrounding the interaction between gut microbiota and COVID-19 drew the attention towards the benefits of (nutraceutical approaches for COVID-19 therapy). The recommended protocol involves administering probiotics, vitamins (mainly vitamins C, D, and E), and trace elements (mainly selenium and zinc). It is also recommended the reduction of caloric intake (carbohydrates and trans-fat or saturated fats) and to replace red meat with fish (omega-3 polyunsaturated fatty acids) and high-fiber plant-based food (Ferreira et al. 2020; Belančić 2020; Tursi and Papa 2020). Moreover, the involvement of nutraceuticals such as polyphenols (flavonoids, phenolic acids, stilbenes, lignans) and spices like curcumin in the diet plan plays a potential role in countering COVID-19 pathways (Infusino et al. 2020).

Cancer

The composition and source of diet are major factors that influence the vitality and composition of microbiota. The worldwide increase in the consumption of sweets, soft drinks, and junk foods leads to changes in the composition of gut microbiota. The consumption of high-carbohydrate low amino acid diet leads to the disturbance of Firmicutes-to-Bacteroidetes ratio. Restricted protein intake was also shown to change the gene expression pattern in the liver and reduce hepatic FXR-FGF15 signaling (Pak et al. 2019; Holmes et al. 2017; El-Sayed et al. 2021). On the other hand, the consumption of low-fiber/high red meat diet alters the intestinal microbiota to favor tumor formation; diet rich in NSP enhances bacterial fermentation/utilization of ingested fibers and the production of short-chain fatty acids (SCFA) such as butyrate, acetate, and propionate. Butyrate and SCFA (in general) are used for energy production by colon epithelium; they exhibit powerful anti-inflammatory effects, required for cell regeneration and the maintenance of a healthy gut barrier (Mutlu et al. 2012; David et al. 2014; Kim et al. 2013; Suzuki et al. 2008). Daily consumption of red meat at high amounts may induce colonic cancer. The microbial lipoperoxidation of heme iron plays a role in carcinogenesis (Martin et al. 2018).

Red meat consumption increases the population of bacterial species involved in the metabolism of amino acids such as Fusobacteria and Alistipes, accompanied by a decrease in the prevalence of those that limit neoplasm induction (SCFA producing species). Supplying the patients with *Lactobacillus* and *Bifidobacterium* species improves the anti-inflammatory anti-carcinogenicity properties (Borges-Canha et al. 2015; Damman et al. 2012; Sokol et al. 2008; Tirandaz and Mohammadi 2013; Veerappan et al. 2012). The role of every species in the enhancement/prevention of cancer development has been studied by many researchers (Moore and Moore 1995; Scanlan et al. 2009).

Fig. 2 The role of microbiota in wide array of disease induction as cancer, obesity, etc.

In addition to red meat, the consumption of processed meat, particularly that fried at very high temperatures, enhances cancer formation due to the production of various mutagenic carcinogenic heterocyclic amines, N-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons (Wu et al. 2006). Meanwhile, the consumption of white meat was seen to be less harmful to red meat. This finding is attributed to the maintenance of microbiota balance in white meat consumers. The beneficial genus *Lactobacillus* was higher in the white meat than in the red meat consumers or even non-meat protein feeders (Zhu et al. 2015).

In addition to red meat, the consumption of fats, especially essential unsaturated fatty acids (n-6 polyunsaturated fatty acids (PUFAs)), plays a critical role in the induction of gastric and colon cancer. The ingested fat enhances cancer by influencing gut flora to metabolize fats to carcinogenic by-products (Lee et al. 2018). It is also believed that a fat-rich diet can stimulate the secretion of high amounts of bile. The bile is then dehydrogenated by anaerobic gut bacteria to produce carcinogenic by-products (Harris 2016).

However, the effect of fat consumption on health status depends on the type of fat consumed as the consumption of good fats like fish oils and omega-3 polyunsaturated fatty acids can protect against colorectal cancer (CRC) (Volpato and Hull 2018). Beside fish oil, other nutritional elements have been found to provide a protective effect against CRC, such as fiber-rich food and high doses of vitamin D or calcium (Thun et al. 2018; Morales-Oyarvide et al. 2016; Harris 2016).

The above-described lifestyle, known as westernized lifestyle (consumption of high meat, high energy, high-fat, and poor-fiber diet) besides smoking and consuming alcohol together, are responsible for the high prevalence of cancer in the Western world (Pelucchi et al. 2011; Marley and Nan 2016; Harris 2016; Bishehsari et al. 2014).

Alcohol consumption is also considered to be a predisposing factor for colon cancer. Alcohol is metabolized in the gut by microflora to produce carcinogenic by-products such as acetaldehyde. Produced acetaldehyde in the gut is responsible for the degradation of folate needed for DNA repair. The permanent deficiency of folate may lead to severe chromosomal damage and neoplasms development (Homann et al. 2000; Duthie 1999).

Besides the role of diet in cancer development, many cancer types may arise following infections or as a result of direct disturbance in the microbiota (e.g., following infection with *Fusobacterium H. pylori*, *Leptotrichia*, and *Campylobacter* species) (Warren et al. 2013) or viral infection (e.g., *human papillomavirus* (HPV), *hepatitis B virus* (HBV) and *hepatitis C virus* (HCV), *Kaposi's sarcoma-associated herpesvirus* (KSHV), *Merkel cell polyomavirus* (MCV)) (Mui et al. 2017; Lunn et al. 2017).

The induction of cancer may also be induced by disturbances in the prevalence/constitution of gut flora. Therefore,

the prevalence of CRC is much higher in the large intestine than in the small intestine. This is attributed to the higher microbial population in the large intestine, especially the gut virome and bacteriophages (Dahiya and Renuka 2017; Sun and Kato 2016). An example of the relationship between present microflora and the type of resulting cancer is infections with *Streptococcus bovis* (SB), which includes *Strep. gallolyticus* (SB type I and II/2) and *Strep. infantarius* (SB type II/1). While the *Strep. gallolyticus* is linked to CRC, *Strep. infantarius* was found to be related to other types of cancer, such as pancreatic and biliary tract tumors (Corredoira et al. 2008a; Corredoira et al. 2008b). SB is a normal inhabitant in the digestive tract of ruminants and can tolerate up to 40% bile concentration. It can also be detected in human fecal samples. Its presence in humans is usually related to serious diseases such as colon carcinoma/ adenoma, inflammatory bowel disease (IBD), endocarditis, or bacteremia (Potter et al. 1998; Dubrow et al. 1991; Nielsen et al. 2007; Sharara et al. 2013; Teitelbaum and Triantafyllopoulou 2006).

Examples of infection-induced neoplasms *Fusobacterium (F) nucleatum* is one of the oral microbiota that can be isolated from stool. Its presence in fecal samples is usually bound to colorectal carcinoma (Tahara et al. 2014; Castellarin et al. 2012).

Although *E. coli* is a normal commensal inhabitant in the human intestinal tract, some isolates acquired mobile genetic elements that harbor various virulence genes and become human pathogens (El Sayed 2000). One of these mobile genetic elements is the pathogenicity island polyketide synthases (pks), which encode colibactin, which is linked to the induction of IBD, Crohn's disease, and even CRC (Buc et al. 2013; Bonnet et al. 2014; Martin et al. 2004).

Even some colonic symbiotes (e.g., *Bacteroides fragilis*), which represent one of the GIT microbiota, produces a zinc-dependent metalloprotease toxin that induces epithelial inflammation, activates cell proliferation, and probably damages the host cell DNA (Goodwin et al. 2011; Wu et al. 2009; Boleij et al. 2015).

Helicobacter pylori (*H. pylori*) is listed as a group 1 carcinogen in the list according to the International Agency for Research on Cancer (IARC) as it induces chronic gastritis, which may result in gastric adenocarcinoma or lymphoid tissue lymphoma. Furthermore, the pathogen's extension to the intestine may also result in CRC (Parkin 2006; Wu et al. 2013; Konturek et al. 2009).

Salmonella infections usually result from consumption of contaminated foodstuffs of animal sources, especially eggs. The infection may turn chronic, and the carrier sheds the bacteria in the feces (Nagaraja and Eslick 2014; Kato et al. 2013). Chronic infection with Salmonella results in persistent inflammation in the GIT, which may develop inflammatory bowel syndrome (IBS), arthritis, or even colorectal and gall bladder

cancer. In parallel, as many members of the clostridial family are incriminated in tumor induction, antibiotic therapy and transplantation of microbiota from healthy individuals have been shown to prevent the development of cancer in tumor-susceptible mice as an animal model (Kumar et al. 2006; Lu et al. 2014; Bongers et al. 2014).

Metabolic diseases

Gut microbiota was found to influence the prevalence of metabolic disorders and general health conditions by mediating the effects of drugs and diet. A low-protein diet improves glycemic control, and metabolic health, increases energy expenditure, and decreases the prevalence of obesity, insulin resistance, and type 2 diabetes. This was attributed to the alteration in gut microbiota at the phylum level and therefore affects liver metabolism (Pak et al. 2019). Gut microbiota may also influence metabolic disorders in a second pathway. Various species of microbiota catalyze the bile acids differently. Bile acids are now known to play a role in fat digestion and as activators of the nuclear hormone receptors. Therefore, the variation in the composition of microbiota consequently leads to variation in the processing of bile acids in the gut, reflecting diverse body activities (Kuipers et al. 2014; Sayin et al. 2013).

An apparent variation in the composition of the microbiota and phenotype of diabetes has been reported in animal models. The alteration in microbiota composition in some instances can enhance insulin resistance and thereby induce type II diabetes. Therefore, recent studies have shown that microbiota transplantation results in a change in susceptibility to metabolic disorders. The tendency for metabolic disorders increases in host harboring microbiota, which can better process dietary sugar and generate hydrophobic bile acids (Kreznar et al. 2017). The main players that determine the occurrence of metabolic disorders among various microbial metabolites in the gut are the SCFA. Insulin sensitivity was positively related to concentration of butyrate.

Similarly, acetate stimulates insulin secretion from the pancreas. However, when SCFA increases, the host will suffer from obesity (Hartstra et al. 2015; Priyadarshini et al. 2015). Examination of microbiota present in the gut of patients suffering from insulin resistance/type 2 diabetes showed a decrease in butyrate-producing bacteria and an increase in bacteria inducing sulfate reduction and oxidative stress resistance (Qin et al. 2012). Although metformin has been used for about 60 years to treat type 2 diabetes, the mechanism of action of metformin could only be understood recently. Metformin was found to alter the gut microbiota in a way that improves glucose tolerance in patients. These findings were confirmed by studying the level of glucose tolerance in germ-free mice that received microbiota obtained from metformin-treated patients (Wu et al. 2017). In addition to their role in the induction of type 2 diabetes, a possible role of microbiota in the induction

of type 1 diabetes has also been reported (Greiner et al. 2014). Based on this, new approaches were developed to treat obesity and diabetes by transplanting microbiota from the gut of healthy individuals into the gut of diabetic people, which leads to the potential sinking of blood glucose levels (Greiner et al. 2014; Zhang et al. 2013).

Obesity

Obesity is defined as excessive fat accumulation to the degree that impairs health. It is primarily, but not exclusively, caused by an energy imbalance between calorie intake and calories expended in the presence of predisposing genetic factors. It may also result from other factors, such as hormonal imbalance (Hill et al. 2012) or disturbance in microbiome composition (mainly the increase in the proportion of Firmicutes accompanied by the decrease in the proportion of Bacteroidetes) (Suzuki and Worobey 2014). Therefore, certain individuals can keep their weight constant despite their high-calorie feed. Present obesity control programs depend mainly on the reduction of energy intake and/or increasing energy expended. This concept ignores the role of other factors, such as insulin resistance and hormonal disturbances (Camacho and Ruppel 2017), and ignores the source of energy in the diet. Weight control programs that do not consider the source of calories usually fail to maintain weight loss. This is attributed to the high demand for energy (175 kCal/day) for the digestion of macronutrients (catabolism), which will not be spent when eating low-fiber high-calorie industrial products (Heymsfield et al. 2012; Feinman and Fine 2004; Jéquier 2002).

According to the WHO, a global obesity epidemic occurred due to the explosive consumption of soft drinks and fast foods among young people, especially between 70th and the 90th (Jaacks et al. 2019). Sugar consumption similarly leads to addiction to drugs do as it leads to the release of dopamine and delays the release of acetylcholine. Repeated and excessive consumption of sugar-rich diets as soft drinks induces behavioral and mental changes similar to those generated in junkies suffering from drug abuse (Hoebel et al. 2009; Avena et al. 2008). Meanwhile, high-calorie diet consumption such as sugar-/fat-rich foodstuffs (ideally sugar-fat combinations such as cookies) has behavioral/neurological and physiological influences such as bulimia and anorexia. This is due to the sharing of behavioral impacts on neural pathways such as the mesolimbic dopamine (DA) system. The release of dopamine represents a rewarding effect similar to addictive behavior (Avena et al. 2009; Davis and Claridge 1998; Volkow et al. 2008; Marrazzi and Luby 1986). Symptoms indicating sugar-addictive potential in animal models are common to drug dependency. They included "Bingeing," "withdrawal signs," "craving," and cross-sensitization, which are attributed to neurochemical changes in the CNS (Avena et al. 2008; Rada et al.

2005). These findings are supported by brain tomography scans, which revealed similar images in both sugar and drug-addicted persons (Wang et al. 2004).

Due to sugar addiction, the global consumption of sugar has increased rapidly in connection with the increase in overweight problems worldwide. Overweight is not only a predisposing factor for heart diseases, metabolic diseases, and joint and backbone diseases, but it has also been found to be linked to at least 13 various types of cancer, including endometrial cancer (Dougan et al. 2015), esophageal adenocarcinoma (Hoyo et al. 2012), gastric cardia cancer, (Chen et al. 2013), liver cancer (Chen et al. 2012), kidney cancer (Sanfilippo et al. 2014; Wang and Xu 2014), multiple myeloma (Wallin and Larsson 2011), meningioma (Niedermaier et al. 2015), pancreatic cancer (Genkinger et al. 2011), CRC, (Ma et al. 2013), gall bladder cancer (Li et al. 2016), breast cancer (Munsell et al. 2014), ovarian cancer (127), and thyroid cancer (Kitahara et al. 2016).

Long-term consumption of a high-protein diet is linked to insulin resistance, diabetes, and cardiovascular disease and enhances the occurrence of certain types of cancer such as colonic cancer. In patients suffering from obesity, shifting their diet to a low-protein diet leads to weight loss, improved insulin sensitivity, and restoration of metabolic health (Pak et al. 2019). Alternatively, the transplantation of microbiota from the gut of healthy people may help solve the problem of obesity (Jéquier 2002).

Liver diseases

Recent studies allied various liver diseases, including non-alcoholic steatohepatitis, liver fibrosis/cirrhosis, and hepatic cancer (hepatic cell carcinoma) with the composition of gut microbiota (Friedman 2013; Guarner and Soriano 2005).

Neural diseases

The interaction between gut microbiota and the development of the nervous system has been investigated by many researchers. It is now clear that the microbiota exerts a long-term influence on the nervous system, starting from birth until aging.

Recent publications have hypothesized that neurodegenerative diseases as multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and even certain psychiatric and neurological diseases as autism and depression could be attributed to functional disorders of the gastrointestinal tract due to alterations and reduction in the diversity of gut microbiota with age (Pellegrini et al. 2018; Hsiao et al. 2013). Additionally, people with limited microbial diversity are found to suffer from poor memory/cognition functions (Verdi et al. 2018) and other neuroinflammatory/neurodegenerative diseases such as traumatic brain injury

and acute ischemia. This is attributed to the breakdown of the gut barrier, allowing pro-inflammatory cytokines and mediators produced by the bacteria to cross the BBB accompanied by immune cells infiltration from the circulation into the CNS, which induces neuronal inflammation, demyelination, and finally damage (Janakiraman and Krishnamoorthy 2018; Kowalski and Mulak 2019; Calvani et al. 2018).

Other diseases

The commensal oral anaerobic bacteria *Fusobacterium nucleatum* has invasive pro-inflammatory properties, which enable them to induce acute and chronic infections all over the digestive tract (Signat et al. 2011). Although these bacteria are normally commensal and have no pathogenic life pattern in the oral cavity, they are associated with cases of Crohn's disease, IBD, and appendicitis (Swidsinski et al. 2011; Strauss et al. 2011).

Role of virome in health and diseases

More than 1200 viral genotypes can be detected in fecal samples of healthy individuals (about 10^8–10^9 VLPs/g feces)(Breitbart et al. 2003; Kim et al. 2011). Virome present in the human gut contains primarily non-pathogenic viruses (Breitbart et al. 2003). This includes plant-derived viruses such as Pepper mild mottle v., *Oat blue dwarf v. and Oat chlorotic stunt v.*, *Tobacco mosaic v.*, *Grapevine asteroid mosaic-associated v.*, *Panicum mosaic v.*, and the *Maize chlorotic mottle v.* Virome also involves many DNA giant viruses (> 300 kb) such as members of *Poxviridae*, *Mimiviridae*, *Asfarviridae*, *Mamaviridae*, *Marseilleviridae*, *Phycodnaviridae*, *Iridoviridae*, and finally the *Ascoviridae*. Additional groups present in the virome include the *Microviridae* family represented by the members: *Microvirus*, *Gokushovirinae*, *Alpavirinae*, and *Pichovirinae* (Scarpellini et al. 2015). In addition to the previously mentioned families, the gut contains another category of viruses that play an essential role in bacterial/pathogen evolution, namely, the bacteriophages (the phagobiota). The phagobiota represents the most abundant members of the human gut microbiome (Duerkop 2018; Dalmasso et al. 2014). Phages are mobile genetic elements that play a major role in transferring virulence genes among the bacterial population. The large genetic diversity and heterogeneity of microbiota and phages enable the phages' continuous adaptation to new usually non-susceptible bacterial hosts. This, in turn, promotes diversification and leads to the continuous evolution of new genotypes and even new pathogens. This phage/bacterial interaction maintains the bacteriophage and microbial diversity in the GIT and may even play a vital role in the induction of

dysbiosis following treatment with antibiotics or certain gut inflammatory diseases (Sordi et al. 2017).

They play a significant role in regulating the bacterial community in the gut and can translocate via the gut mucosa to lymph/internal organs. Therefore, they can play an additional immunoregulatory role. Some can share in disease induction; others possibly have a protective role in the gut (Łusiak-Szelachowska et al. 2017).

In the very early life of infants, the variety of gut bacteriophages is usually great with a clear dominance of the DNA phages from the order *Caudovirales*. Later on, the composition shifts and the variety decreases where the members of the family *Microviridae* begin to dominate. The alteration in virobiota composition and the speed of these shifts depends mainly on the feed and will have great consequences on the microbiota and, consequently, on human health later in life (Lim et al. 2016).

Generally, bacteriophages can be grouped into two major groups according to their lifestyle, lytic phages that kill the bacteria after infection to produce virions. The second type is known as lysogenic phages that integrate their DNA in the bacterial genome and replicate passively with the bacteria. As bacteriophages are host-specific, they selectively infect and kill only susceptible bacterial species (El Sayed 2000). This may lead to a decrease in bacterial diversity and, therefore, indirectly induce certain human diseases such as IBD and even certain oral diseases (Norman et al. 2015; Ly et al. 2014).

Phage induction can be induced in many ways, which subject the bacteria to stress conditions such as administering certain antibiotics that stimulate the SOS signals in lysogenic bacteriophages. As a result, the transcription of late genes starts and results in increased phage integrase DNA within the gut phage community. Phage induction leads to the death of hosting bacteria and the release of billions of bacteriophages simultaneously. This, in turn, has consequences like disturbances in the bacterial equilibrium among symbionts to pathobionts in the gut, transmission of mobile genetic elements among the related bacterial species, evolution of new pathogens, and possibly intestinal dysbiosis (Johnson et al. 2017; Ghaisas et al. 2016; Allen et al. 2011).

In general, phage induction can be influenced by nutrient availability. The effect of diet on bacteriophage populations can be clearly seen when shifting from a low-fat diet to a high-fat diet (Howe et al. 2016). Bacterial lysis also leads to local inflammation in the intestinal epithelium due to the release of bacterial proteins, lipids, and DNA (Manrique et al. 2016). The released bacteriophages may also penetrate the gut mucosa and migrate via blood/lymphatics towards the immune tissues (Górski et al. 2006). Under certain circumstances, the mucin covering the mucous membranes of the GIT may trap bacteriophages through a mechanism known as bacteriophage adherence to mucin (BAM), where capsids of certain phages

contain immunoglobulin (Ig)-like domains, which can adhere to the host mucin. Their intestinal mucosa position allows them to act as a guard offering protection against invading bacteria (Barr et al. 2013; Minot et al. 2012). The interaction between phages and mammalian cells is not limited to their adhesion to mucus membranes. The phages may be endocytosed by the epithelial lining and again exit from them. The necked phage DNA may be present uncoated inside the cells (Nguyen et al. 2017; Lehti et al. 2017).

The composition of the phages population in the gut is affected by many factors, particularly those affecting gut microflora composition, such as the host diet. For example, the availability of amino acids promotes the induction of φV1/7 bacteriophage in *E. faecalis,* which seems to be a mechanism by which *E. faecalis dominates over other related bacteria in the GIT (*Duerkop et al. 2012*)*.

Disease induction by virome

The presence/absence or the alteration of the phage community in the gut may be linked to disease conditions. The increase in their population or change in their composition leads to inflammation of the gut and induction of inflammatory bowel diseases. Alteration in their composition may also lead to type 1 diabetes in children (Zhao et al. 2017; Wagner et al. 2013).

Bacteriophages have been shown to induce IBD through the reduction of bacterial diversity in the gut. A direct role in disease induction was also suspected (Lucas López et al. 2017; Dalmasso et al. 2014). Beside IBD, phages have also incriminated in the induction of other bowel diseases such as Crohn's disease (Wagner et al. 2013; Norman et al. 2015) or even metabolic diseases besides their role as immune modulators (Burcelin 2016).

Phages were also found to influence human health by increasing gut permeability (leaky gut) and lead to the impairment of the intestinal barrier (Tetz and Tetz 2018; Tetz and Tetz 2016; Lawrence et al. 2019). This, in turn, leads to the escape of toxins into circulation and inflammatory mediators' production (Bischoff et al. 2014; Fang 2016). Bacteriophages can also directly interfere with the immune system and, by so doing, enhance bacterial infections (Sweere et al. 2019). In addition, the presence of prion-like domains in bacteriophages is thought to play a role in their virulence (Hasegawa et al. 2017; Tetz and Tetz 2017).

The ingestion of bacteriophages with the diet leads to mass destruction of bacteria in the gut. This, in turn, leads to the release of high amounts of bacterial DNA in the circulation and elevates the pathogen-associated molecular pattern (PAMP). Beside the bacterial DNA, free bacteriophage particles, fractions of bacterial LP, amyloid, and other bacterial antigens may enter the circulation. All these elements increase

the gut permeability (leaky gut) and irritate the immune system, resulting in the induction of autoimmune diseases, neurodegenerative diseases, and other serious diseases (Aas et al. 2008; Sursal et al. 2013; Wang et al. 2015; de Paepe et al. 2014; Anunobi et al. 2018).

Bacteriophages in the CSF have been reported to induce neurodegenerative such as multiple sclerosis (MS) and autoimmune diseases. This link between the presence of phages in CSF and neurodegenerative diseases is supported by the fact that MS patients suffer additionally from leaky gut and a disrupted BBB, which facilitates phage transmission from the gut to the brain (Tetz and Tetz 2018; McManus and Heneka 2017; Zhou et al. 2013).

The possible role of lytic phages in the induction of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases or amyotrophic lateral sclerosis was documented. Patients who have Parkinson's disease showed 10-fold higher concentrations of *Lactococcus lytic phages with a severe reduction in the lactococci population in the gut. This is attributed to the killing effect of available c2-like and 936 groups of phages on the Lactococci. The virulent (Abi-escape phage mutants) were provided through dairy products (*Tetz et al. 2018; Bäuerl et al. 2018; Braak et al. 2003; Scheperjans 2016).

Medical uses of bacteriophages

It was surprising that short-term oral administration of narrow-spectrum antibiotics did not influence the composition of phages/viruses in the gut. However, it affected the composition of the available bacteria (Ly et al. 2016). Although the treatment of patients with certain antibiotics increases the number of free *Clostridium difficile* and *P. aeruginosa* bacteriophages in human feces and sputum, respectively, according to some reports (Fothergill et al. 2011; Thomas 1966), due to the growing challenge of antibiotic resistance among pathogenic bacteria, alternative therapeutic possibilities via phage therapy are being investigated. The phages can infect and lyse the bacteria; in addition, they collaborate with the immune system to clear the invading bacteria. Additional applications of phages in gene therapy are under development at the time (Roach et al. 2017).

Conclusion

The influence of microbiota on our health/disease status is underestimated. Various infectious and non-infectious diseases can be induced by disturbances in the composition, prevalence, and vitality of the microbiota. Manipulation of external factors such as the nature of diet and lifestyle can

re-establish the balance among microbiota populations in order to prevent or even treat such diseases. The role played by microbiota in health and disease was highlighted during the COVID-19 pandemic. Nutraceutical non-pharmacological therapeutic and prophylactic approaches could reduce the mortality rate, the diseases severity, and serious complications. The use of probiotics, dietary supplements, and microbiota transplantation from healthy individuals are promising future therapeutic trends for several infectious and non-infectious diseases.

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