Microbiota and epigenetics: promising therapeutic approaches?

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Abstract

The direct/indirect responsibility of the gut microbiome in disease induction in and outside the digestive tract is well studied. These results are usually from the overpopulation of certain species on the cost of others, interaction with beneficial microflora, interference with normal epigenetic control mechanisms, or suppression of the immune system. Consequently, it is theoretically possible to cure such disorders by rebalancing the microbiome inside our bodies. This can be achieved by changing the lifestyle pattern and diet or by supplementation with beneficial bacteria or their metabolites. Various approaches have been explored to manipulate the normal microbial inhabitants, including nutraceutical, supplementations with prebiotics, probiotics, postbiotics, synbiotics, and antibiotics, or through microbiome transplantation (fecal, skin, or vaginal microbiome transplantation). In the present review, the interaction between the microbiome and epigenetics and their role in disease induction is discussed. Possible future therapeutic approaches via the reestablishment of equilibrium in our internal micro-ecosystem are also highlighted.

Keywords Epigenetic · Fecal microbiota transplantation · FMT · Microbiome

Introduction

Microbiome (microbiota) is an expression that describes the community of [microorganisms](#) that inhabit the human/animal body. They live together with their hosts in a complex interacting micro-ecosystem. The microbiome consists of trillions of commensals and symbiotic bacteria, viruses, protozoa, and yeast. All these species together serve as virtual

endocrine organs in our bodies (Clarke et al. [2014](#)). The microbiota and its metabolites play a potential role in the regulation and maintenance of normal host physiology, behavior, and even in host immunity as a part of the GIT. This was seen in animal experiments where the defensive role of microglia was compared in normal vs SPF mice following viral infection targeting the CNS (Brown et al. [2019](#)). Although the gut microbiota varies among populations, a core microbiome (about 40% of the total microbiota) remains constant among individuals (Turnbaugh et al. [2009](#)). Therefore, dysbiosis of gut microflora usually leads to intestinal/extra-intestinal pathological disorders, including GIT inflammatory disorders, metabolic diseases, and various cardiovascular disorders (Kamada et al. [2013](#)). Changes in the normal microbial content or composition inside the hosts result in an alteration of the health status of the individual (El-Sayed et al. [2021a](#)). For instance, prenatal exposure to antibiotics or in the very early life decreases the diversity of gut microbiota and results in obesity later in life (Torp Austvoll et al. [2020](#)). This interaction takes place in direct or indirect ways. One of these mechanisms is through their effect on gene regulation and host epigenome. Epigenetics focus on studying changes in gene expression pattern without modifying the DNA sequence (Torp Austvoll et al. [2020](#)). In fact, epigenetic modifications are natural defense mechanisms for DNA repair and cell differentiation which represent the cell memory that back up cellular responses to environmental events (Greer and Shi [2012](#);

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Key points

- 1- Quantity or quality of the diet can directly or indirectly affect the microbiome and epigenetics.
- 2- Epigenetic modulations and our microbiome have an important role in the induction of diseases.
- 3- Safe and efficient therapeutic approaches via microbiome transplantation could be a solution for serious chronic diseases.
- 4- Supplementation with pre-, pro-, or postbiotics opens the door as safe and efficient therapeutic strategies for serious diseases.

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Henikoff and Greally 2016; Saradalekshmi et al. 2014). The delivered data in the last decades which discuss the role of epigenetic gene regulation in health and disease expanded our understanding of the development of several diseases such as metabolic diseases, obesity, cancer, or autism. It is now clear how the cells can differentiate into different cell types although they originate from one fertilized cell and share the same genome/genes. The epigenome is usually influenced by external environmental factors in addition to internal factors such as the microbiome which consists of 100 trillion of microbes and represents 90% of our DNA (El-Sayed et al. 2021a; Yen et al. 2016). The permanent exposure of our immune system to different microbes in our environment facilitated the co-evolution of both gut microbiota and immune system and established a state of equilibrium. Therefore, changes in the internal microenvironment in the gut (e.g., due to change in diet or lifestyle) usually result in the disturbance in gut microbiota homeostasis known as dysbiosis. Similarly, changes in the external environment lead to a reduction of microbial biodiversity/gut dysbiosis (e.g., due to pollution or climatic changes) which consequently leads to modifications of chromatin structure associated with epigenetic up/downregulation of gene expression (Haque et al. 2021; Torp Austvoll et al. 2020). Epigenetic gene regulation is usually achieved via several mechanisms such as histone acetylation, DNA methylation/demethylation, miRNA, and small non-coding RNA (Greer and Shi 2012; Yen et al. 2016). When enough epigenetic epimutations accumulate in the cells, disturbance of the balanced homeostasis regulating cell apoptosis and cell proliferation starts to occur and the cells start to undergo carcinogenic changes which explain the close interactive relationship among microbiome, epigenetics, and malignancy (El-Sayed et al. 2021a). The present work discusses the interaction nexus among three related subjects (microbiota, diet, and epigenetics) separately or collectively, i.e., the interaction between (1) microbiota and host, (2) the microbiota, epigenetic and diet, and finally (3) the role of microbiota in the induction/treatment of epigenetic diseases. Taking such correlations into consideration enables a better understanding of disease pathogenesis and opens the door for the development of novel therapeutic approaches using microbiota transplantation or through the administration of pro-, pre-, post-, or synbiotics. The modulation of the epigenetic profile to treat epigenetic induced diseases via the use of nutraceutical and microbiota is not only safer and more economic than the use of chemical-based medications, but it also enables the improvement of hardly curable diseases as cancer and autism.

Interaction between microbiota and host

The composition and biodiversity of the microbiome were shown to vary based on diverse factors which can be related

to (1) the host (e.g., genetic factors, way of birth and history of breastfeeding, age, vaccination history, health status and infections, medication, hygiene, life style, smoking, alcohol consumption, and geographic location), (2) internal microenvironment (e.g., Redox potential, oxygen level, stress, pH, bile acids, and immune status), and (3) the microbiota (e.g., microbial competition, adhesion to the mucous membrane, production of persistent pro-inflammatory reactions, and nature of microbial metabolites) (El-Sayed et al. 2021a; Haque et al. 2021).

The microbiome are usually in a state of continuous and balanced interaction with their hosts. Previous reports classified this interaction according to the influenced system/organ into (gut-brain axis), (gut-liver axis), (gut–renal/heart axis), and so on (Larsen et al. 2010). Accumulating evidence proves the presence of the Gut-Brain Interaction/axis characterized by a bidirectional communication network which is disrupted in the case of dysbiosis (Carabotti et al. 2015). The clear and potent influence of gut microbiota on the development of CNS and the maintenance of its function supports this hypothesis. Leaky gut increases the passage of toxins and metabolites into the circulation, such substances influence mostly the neuroimmune and neuroendocrine axis and, by so doing, negatively affect the development of the CNS. This mechanism is involved in the pathogenesis of autism, according to several reports (Angelis et al. 2015; Fowlie et al. 2018; Siniscalco et al. 2018).

The overpopulation of certain gut gram-negative gut commensals leads to the production and absorption of high amounts of their endotoxins (lipopolysaccharide/LPS; present in the outer membranes of gram-negative bacteria). The released immune response against these LPS is linked to the induction of chronic depression status and other neurodegenerative diseases in humans (Diaz Heijtz et al. 2011; Maes et al. 2012). These data were supported by the finding of animal experiments that indicated the role of absorbed LPS in the circulation in the induction of neurodegeneration. Such cases were manifested by deterioration in neurogenic functionality due to the aggregation of α -synuclein and the well as loss of dopaminergic neurons from the substantia nigra. Beside their role in neurodegeneration, higher blood levels of LPS were also related to cases suffering from severe autism, hepatic cirrhosis, metabolic diseases/diabetes, cardiovascular disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and finally autoimmune diseases (Brown 2019). The exerted effects can be (1) direct effects (e.g., via reprogramming of the hypothalamus-pituitary–adrenal axis neurotrophic products), which can result in behavioral changes, including anxiety and depression, or (2) indirectly by altering the central gamma-aminobutyrate (GABA) receptor expression (Bravo et al. 2011; Diaz Heijtz et al. 2011; Sudo et al. 2004).

Similarly, several hepatic, renal, and cardiovascular diseases may be induced by bacterial metabolites. The gut-liver

interaction/axis gets increasing attention. The interaction was proven to be linked to gut microbiota and their metabolites, which are absorbed from the intestine and transported to the liver through hepatic portal circulation (Aron-Wisniewsky et al. 2013). A good example of hepatic disorders is the induction of nonalcoholic fatty liver by the metabolism of choline by overgrown gut microbiota. It is worth mentioning that the disease can be improved after treatment with metronidazole. The metabolites of choline lead not only to the inability to synthesize phosphatidylcholine, to the accumulation of triglycerides in the liver, but also to cardiovascular disease (CVD) (Corbin and Zeisel 2012; Drenick et al. 1982; Dumas et al. 2006; Wang et al. 2011).

One of the methods to manipulate the gut microbiota to establish or disturb the equilibrium in the gut is by changing the diet quality/quantity. This is shown to have a significant positive/negative influence on health. For example, good carbohydrates (high fiber content with low glycemic index) against bad carbohydrates, good fats (rich in omega 3) against bad ones (rich with omega 6, polysaturated/hydrogenated oils) (Hills et al. 2019; Reynolds et al. 2019).

Ingested fibers are usually fermented by gut anaerobes into SCFAs which usually cover 60–70% of the energy requirements of the colonocytes (Roediger 1982). The remaining SCFA that were not utilized were transported via the circulation to the liver where they aid in glucose/insulin regulation (den Besten et al. 2013). Therefore, the released SCFA in the gut has a positive impact on insulin resistance and the prevention of type 2 diabetes (Weickert and Pfeiffer 2018). SCFAs exert their role through various mechanisms, including epigenetic modulations. They stimulate histone hyperacetylation and the changes in gene expression patterns. These in turn enhance apoptosis and stop cell division with potent anti-inflammatory effects. This is achieved through the dual action on both FFAR3 and FFAR2 receptors (Brown et al. 2003; Layden et al. 2013; Schilderink et al. 2013). The change in the nature of diet, therefore, can be applied to treat certain diseases. According to published reports, the change in diet of children suffering from epilepsy to a ketogenic regime could decrease epileptic attacks by 50% (Olson et al. 2018; Reddel et al. 2019; Wheless 2010). This is attributed to the direct effect of released ketone bodies on both the CNS and gut microbiota, in particular the genera *Akkermansia* and *Parabacteroides*. Therefore, running studies are investigating the possible therapeutic effect of a ketogenic diet on other disorders of the CNS, including autism, Alzheimer's, and Parkinson's disease (Hills et al. 2019).

Akkermansia muciniphila is a normal inhabitant of the gut. As a mucin-eroding bacterium, it is important for normal mucin turnover in the gut. However, consumption of a diet poor in fiber content enhances the overgrowth of *Akkermansia muciniphila* which results in severe degradation of the mucin layer lining the gut. This leads to gut leakage and an increase

in intestinal permeability and allows the passage of toxins, bacterial LPS, and even pathogenic bacteria to the circulation (Desai et al. 2016; Grander et al. 2018).

Interaction among diet-microbiome-epigenetics

Diet has a great influence on the composition of microbiota. For instance, the biodiversity of the microbiota is affected by the concentration of protein/fat/carbohydrate in the diet, the type of consumed fats and carbohydrates, alcohol consumption, antibiotic residues/chemical pollutants in diet, and degree of food processing (El-Sayed and Kamel 2021 #3503). Published reports have accumulated clear evidence about the interaction among the three corners of the triangle (diet-microbiome-epigenetics). The change in the quantity or quality of the diet can directly or indirectly affect the other two factors, for example, the relationship between high consumption of red meat and the development of colonic cancer. The haem favors the multiplication of certain bacterial species (e.g., *Fusobacteria* and *Alistipes*) on the cost of other species (e.g., SCFA producing species). The overpopulation of these bacteria metabolizes the residues of red meat in the gut and produces carcinogenic metabolites. These metabolic byproducts induce colorectal cancer through epigenetic modulatory pathways (Borges-Canha et al. 2015; Damman et al. 2012; Martin et al. 2018; Xu et al. 2015). The consumption of meat products, which are usually rich in chondroitin sulfate, enhances the growth of *Bacteroides thetaiotaomicron* (sulfatase screening) and *Desulfovibrio piger* (sulfate-reducing) bacteria (Rey et al. 2013). At the same time, the high concentration of the haem present in the red meat stimulates hyperproliferation of the gut epithelium and disturbs the microbial ecosystem (Ijssennagger et al. 2015) if the diet is based on high manufactured red meat combined with low fibers diet, all *Bacteroides thetaiotaomicron*, *Desulfovibrio piger*, and *Akkermansia muciniphila* will flourish and stimulate the induction of type II diabetes. This process can be counteracted by consuming high fibers diet (Consortium 2015; Wang et al. 2017). It is worth to notice that not only the diet can influence the composition of gut microbiota, but also the type and quality of drinking water. Microbial content in Bama mineral water was found to be able to re-shape the gut microbiome. Many health advantages have been reported as a result of Bama water-based microbiome reshaping, including the prevention of breast cancer, increase of life span, and repair of damaged DNA and mitochondria (Chen et al. 2018). Mineral water in general that contains high concentrations of sodium can improve insulin resistance in postmenopausal women. Meanwhile, drinking bicarbonate-rich mineral water decreases the prevalence of T2D through the enhancement of the gut bacteria *Christensenellaceae*. It is worth to notice that

the transplantation of *Christensenella minutia* reduces weight gain in animal experiments (Goodrich et al. 2014; Schoppen et al. 2007).

Autism is another good example not only to present the influence of microbiota on the epigenome to develop diseases but also to demonstrate how the situation can be improved through the correction of microbiome via nutraceuticals (Sabit et al. 2021; Zheng et al. 2020). In autistic patients, the disturbance in gut microbiota induces epigenetic changes in the brain methylation profile (via the gut-brain axis) and initiates chromatin remodeling. The restoration of the autisms associated epigenetic changes can improve the condition. This can be achieved by the conversion of the disturbed cellular methylation pathways through the correction of gut microbiome (for instance by probiotics, or via the consumption of **sulforaphane** (broccoli), folate derivatives, or ketogenic diet) (Baribeau and Anagnostou 2021; Eshraghi et al. 2020; Tan et al. 2021). The use of nutritional substances to cure or mild the clinical signs of diseases is called Nutria-epigenomics. This branch of science was developed to investigate the interaction between diet and epigenetics, and how to use diet to correct health disorders resulting from epigenetic modulations. Meanwhile, the term nutraceuticals was also developed to describe foodstuffs that provide medical/health benefits and can be used to prevent/treat certain diseases (Hwang and Lim 2015; Li 2018; Waterland and Jirtle 2003). One of the most studied substances is sulforaphane (present in broccoli). In our bodies, sulforaphane acts as a histone deacetylase inhibitor and regulates the expression of many genes in the Nrf2 pathway. Clinical investigations have reported the role of sulforaphane in the prevention of cancer and atherosclerosis, the treatment of Alzheimer's disease, and the improvement of clinical signs related to autism (Clarke et al. 2008; Li et al. 2015b; Lynch et al. 2017; Myzak et al. 2007; Sutaria et al. 2012; Yang et al. 2016; Zhang et al. 2017).

Similarly, genistein (present in leguminous plants and soybeans), epigallocatechin-3-gallate (in green tea), and resveratrol (in grapes) have anti-cancer effects (Kim et al. 2017; Pastoriza et al. 2017; Paul et al. 2017). Furthermore, melatonin (in grapes and nuts), curcumin (Curcuma), Indole-3-carbinol (cruciferous vegetables), lycopene (grapefruits), garcinol (*Garcinia indica* fruit), and apigenin (artichokes) are potent anti-inflammatory. However, the same substances may have several therapeutic effects, e.g., genistein, Indole-3-carbinol, and melatonin have additional hepatoprotective potential, while sulforaphane has neuroprotective properties (Behera et al. 2016; Catanzaro et al. 2018; Hanedan Uslu et al. 2019; Lee et al. 2018a; Wu et al. 2017). The anti-cancer effect was shown to be attributed to their epigenetic modulatory effect besides their effect on gut microbiota to activate cell apoptosis mechanisms (Cohen et al. 2000; García-Villalba et al. 2013; Wu et al. 2019; Yang et al. 2007).

Epigenetic adaptations to the environment are important for the survival and best performance of organisms. They are evolved to sustain specific, stable, and better control of genomic regulations by controlling gene expression. Epigenetic modifications are not limited to eukaryotes, they may occur in bacteria, plants, fungi, invertebrates, and vertebrates. In bacteria, the modifications take place in the bacterial genome by DNA **adenine** (instead of **cytosine**) methylation. Epigenetic modifications are important for bacterial virulence, such as in *Streptococcus pneumoniae* (the pneumococcus). The epigenetic switch allows the bacteria to change their virulence determinants among six alternative profiles randomly according to variable methylation systems. These six profiles have different virulence levels (Manso et al. 2014). Epigenetic modulations are affected by both internal stimuli (e.g., mutations, metabolic pathways, neurohormonal control mechanisms, in addition to factors related to age and health status) and external factors (diet, medication, pollution, lifestyle, sport, and stress) (Pal and Tyler 2016; Remely et al. 2015; Youngson and Morris 2013).

In eukaryotes, epigenetic regulations are able to reprogram differentiated cells in response to environmental changes. Misprogramming of the cells may lead to serious diseases, including chronic, degenerative, and inflammatory diseases such as various cancer types, kidney diseases, obesity, diabetes, osteoporosis, and neurodegenerative diseases (Berger et al. 2009; Lopomo et al. 2016; Ostanek et al. 2018). Abnormal epigenetic disturbances may result from bacterial invasion. The pathogens induce such changes in the host cells to suppress their immune response and therefore enable their survival (J Dunne et al. 2015).

Unlike genomic mutations, epigenomic risk markers can be re-modified and have the potential to be reversed. Epigenetic studies are important to explore robust epigenetic biomarkers which enable the prediction of future metabolic health problems and to understand the pathogenesis of metabolic disorders for their avoidance (Milagro et al. 2013). In addition, a better understanding of influencing factors and the mechanisms of epigenetic machinery will enable the enhancement of the development of therapeutic tools that can reverse epigenetic anomalies (Sharma et al. 2010).

Environmental signals that affect the organism usually take place during the embryonic/fetal period. It was shown that the environmental stimuli during the perinatal period play an important role in the programming of human organs throughout his life. Although obesity is a metabolic disease that was declared by the WHO to be a global pandemic, the role of modifications on epigenetic marks was described, whereas altered methylation and/or histone acetylation levels were reported in genes responsible for metabolic processes (Burgio et al. 2015; Lopomo et al. 2016).

Microbiome-induced diseases

The variation in microbiome profile among healthy persons and those suffering from benign or malignant tumors strengthened early reports about the possible role of microbiota in the induction and development of carcinogenesis and determine their degree of aggressiveness (Meng et al. 2018; Xue et al. 2018). As previously mentioned, the diet influences the composition of microbiota and health status through various mechanisms. For instance, a low fiber high-fat diet can induce serious undesired changes in the composition of gut microbiota and enhances oncogenic changes. This is attributed to (1) the bulky effect of fibers and their regulation of food passage in the colon decreases food fermentation in large intestine, minimizes the contact time between mucosa and harmful metabolites and reduces their absorption to circulation, (2) microbial digestion of fibers releases short-chain fatty acids which change the gut pH and epigenetically modulate gene expression pattern, (3) the continuous production of butyrate as by-product of microbial fiber digestion inhibits uncontrolled cell division and enhances apoptosis, and finally (4) the ingestion of high-fat diet increases bile production. In the colon, undigested fats and unabsorbed bile are metabolized by gut microbiota to produce carcinogenic metabolites (El-Sayed et al. 2021a). The disturbance in microbiota can lead not only to gastrointestinal cancer but also to extra-intestinal ones. One of the best examples of the microbiota-related extra-intestinal neoplasm is breast cancer, where women with or without breast cancer have different local breast microbiome profiles (Chen et al. 2019; Wang et al. 2014). Beside the breast microbiome, gut microbiota were also found to influence breast cancer through metabolism of estrogens and other hormones which leads to disturbances in hormone levels in the circulation (Armstrong et al. 2018; Goedert et al. 2018). The aggressiveness/invasiveness of breast cancer was shown to be correlated with the reduction in the methylobacterium population (Fernández et al. 2018). A high-fat diet accompanied by alcohol consumption is strongly linked to breast cancer (Blackburn and Wang 2007; Boffetta et al. 2006; Hills et al. 2019). In addition to breast cancer, a clear relationship between microbiota and other cancer types was described in the literature where the microbiome is involved directly/indirectly, completely/partially in the induction of different cancer types affecting the digestive tract (Borges-Canha et al. 2015; Dahiya and Renuka 2017; Fernández et al. 2018; Lee et al. 2018b; Martin et al. 2018; Sun and Kato 2016). For instance, gastric cancer may result from persistent bacterial (e.g., *H. pylori*) adhesion to the gastric mucosa which maintains a persistent inflammatory process and leads to epigenetic and oncogenic changes in the gastric mucous membrane. Meanwhile, oral cancer may develop as a consequence of bad oral hygiene, smoking, or alcohol consumption which alter the microenvironment of the oral microbiome.

Similarly, the metabolism of alcohol by oral microbiota to produce acetaldehyde interferes with DNA repair and enhances chromosomal damage. In addition to the role of gut and breast microbiome in cancer pathogenesis, disturbances in bladder, ovarian, vaginal, uterine, male genital tract, and pulmonary microbiome can also initiate local carcinogenicity (El-Sayed et al. 2021a; Haque et al. 2021; Lu et al. 2020; Perrone et al. 2021; Thomas et al. 2021; Tuominen et al. 2021), and in addition to the role of some microbiota in cancer development, many members of our virome are also incriminated in triggering various types of cancers (Haque et al. 2021). It is of high interest that the microbiota not only induce cancer but they can also interact with cancer therapeutic protocols. For instance, the used chemotherapeutic preparations such as gemcitabine can be metabolized and inactivated by Gammaproteobacteria which can be counteracted by the concurrent administration of antibiotics (e.g., ciprofloxacin). On the other hand, cyclophosphamide can only exert its anti-cancer effect through translocation of certain gut microbes to other lymphoid organs to activate the physiological anti-cancer immune response mainly T helper 17 (pTH17) and TH1 cells. Similarly, a successful treatment of cancer with Ipilimumab or immune checkpoint inhibitors (ICIs) requires a balanced gut microbiome (El-Sayed et al. 2021a).

In addition to cancer, the microbiome is linked directly with metabolic disorders (including obesity, insulin resistance, and type 2 diabetes) (Hartstra et al. 2015; Kreznar et al. 2017; Pak et al. 2019; Priyadarshini et al. 2015; Sayin et al. 2013), liver diseases (Friedman 2013; Guarner and Soriano 2005), neural and psychological disorders (Hsiao et al. 2013; Janakiraman and Krishnamoorthy 2018; Kowalski and Mulak 2019; Pellegrini et al. 2018), Crohn's disease, IBD, and appendicitis (Strauss et al. 2011; Swidsinski et al. 2011), and inhibition of immune system response to pathogens (Sweere et al. 2019). Other microbiota which live outside the gut are also involved in disease induction, such as the role of oral inhabitants in the induction of CVDs, atherosclerosis, Alzheimer's disease type 2 diabetes, and cancer (Carter et al. 2017; Olsen and Yilmaz 2019). A clear link between gut microbiota and obesity has been established. The microbiota present in the gut of obese humans can better harvest energy from the diet through the production of SCFA. Besides being a direct source of energy, SCFAs are also signaling molecules that modulate gene expression patterns to decrease gut transit time and promote obesity (Samuel et al. 2008; Turnbaugh et al. 2006). In animal experiments, microbiota were found to directly interfere with host genes responsible for lipid metabolism (e.g., *Fiaf* gene) (Bäckhed et al. 2007). Obesity can also result from decreased diversity and disturbance of balance in the gut microenvironment due to changes in diet or the use of antibiotics (e.g., when the Firmicutes: Bacteroidetes ratio increases) (Ianiro et al. 2016; Ley et al. 2005). It is also worthy to mention that the

physio-pathological changes associated with alteration of normal microbiota can increase the susceptibility to infectious diseases such as COVID 19. Gut microbiota were found to upregulate the production of ACE receptors and by so doing facilitate virus adhesion to target cells. The administration of oral probiotic formulation increased the survival of hospitalized COVID 19 patients (El-Sayed et al. 2021b; Walton et al. 2021).

Role of microbiota in protection from diseases

The microbiome plays an important role in the maintenance of healthy physiological, immunological, and neurological host status. They help in energy housekeeping, supplying the host with vitamins and useful metabolites. In addition, they defend the host against invasion and colonization by pathogens; therefore, disturbance of the equilibrium in the gut ecosystem leads to various gastrointestinal and systemic diseases (Nicholson et al. 2012; Wilson and Nicholson 2015).

The host-microbe interaction is very complex. It is of high interest to know that the role of the microbes depends not only on their species, abundance, or viability but also on their location. For instance, the microbiome located in the small intestinal crypts controls the proliferation of enterocytes by regulating gene expression and DNA replication. Meanwhile, those located at the tip of the villi are responsible for the regulation of metabolic and immunogenic aspects (Olszak et al. 2012). On the other hand, the enterocytes interact with the microbial population lead to colonization by regulating the production of mucin and many antibacterial substances (Pelaseyed et al. 2014).

Microbial metabolites also play an essential role in the regulation of mucosal immune response. For instance, SCFAs are not only an important source of energy for the gut epithelium, but are also for the regulation of intestinal motility, downregulation of inflammation, and strengthening of tight epithelial cell junctions (Furusawa et al. 2013; Maslowski et al. 2009; Smith et al. 2013). Another example of beneficial metabolites is the secondary bile acids resulting from the metabolism of bile acids by the microbiota (Kawamata et al. 2003). Many of the genes which play a role in IBD/Crohn's disease (e.g., NOD2 and ATG16L1) are to variable extent regulated by host-microbe interaction (Cho 2008). While fecal microbiome transplantation (FMT) from healthy individuals to IBD patients improves the situation, the reverse FMT from IBD into healthy individuals increases their susceptibility to develop IBD (Elinav et al. 2011).

The microbiota play an important role in the protection against pathogenic infections, which represents a safe alternative for the treatment of antibiotic-resistant pathogens, e.g., the vancomycin-resistant enterococci can be cleared from the GIT through the administration of *Enterococcus faecalis*, or the

treatment of antibiotic-resistant *Staph. aureus* with commensal strains of *Staphylococcus lugdunensis* (Kommineni et al. 2015). This can be achieved either through various mechanisms including (1) immune system-mediated or non-immune-derived mechanisms, among these (A) simple competition for the available nutrients, e.g., the competition between non-pathogenic gut inhabitants with pathogens such as STEC (*E.coli* O157) or *C. rodentium* for the available sugars or with *Salmonella typhimurium* for iron (Deriu et al. 2013; Kamada et al. 2012; Maltby et al. 2013), and (B) production of biologically active organic acids, bacteriostatic/bactericidal molecules which kill, inhibit, or prevent colonization of pathogenic bacteria. The best examples for this group are the bacteriocins produced by gram positive bacteria (e.g., the production of bacteriocin by *Bacillus thuringiensis*, which has potent bactericidal activity against *Clostridium difficile*), and the production of microcins by gram-negative bacteria (e.g., by *E.coli* strain Nissle 1917 and used to control *Salmonella typhimurium* infections) (Rea et al. 2011). Similarly, SCFA, which are excreted as microbial metabolites by fibrolytic anaerobic bacteria, showed a potential inhibitory effect against *E. coli* O157 colonization in the gut (Sassone-Corsi et al. 2016; Shin et al. 2002; Zipperer et al. 2016), (C) through interference with vital gene expression in pathogenic bacteria, e.g., the stimulation of quorum-sensing signal AI-2 production by *Ruminococcus obeum* inhibits mucosal colonization by *Vibrio cholerae* (Hsiao et al. 2014), (D) changing the environment to be unsuitable for the survival of the pathogens, e.g., the SCFA changes the gut pH and by so doing downregulates virulence genes present in *Salmonella typhimurium* and inhibits its invasion to the intestinal mucosa, or *Clostridium scidens* converts the primary bile acids in the gut to secondary acids, which interfere with *C.difficile* survival (Buffie et al. 2015; Lawhon et al. 2002). Similarly, through the production of high amounts of acetic acid and lowering the pH, Bifidobacteria bacteria can inhibit the expression of the *stx* gene responsible for the production of Shiga toxin by *E. coli* O157: H7 strains (Asahara et al. 2004). (E) The microbiota plays a role in the production of mucin (the first line of defense in the intestine) and the underlying antimicrobial peptides. The mucus layer in GF mice is thinner and chemically different than in normal mice; they have smaller mesenteric LNs and less efficient lymphocyte binding capacity. They also have smaller Peyer's patches. All these malformations make them more sensitive to pathogen invasion than that in normal mice (Bouskra et al. 2008; Deplancke and Gaskins 2001; Frantz et al. 2012; Johansson et al. 2015; Lécuyer et al. 2014; Pabst et al. 2006; Pabst et al. 2005; Vaishnava et al. 2008). (F) Adsorption of toxins or the reduction of gut permeability to bacterial toxins: this is seen as an example in the yeast cell wall, which can adsorb mycotoxins and by so doing protect against their harmful effects. Similarly, some Bifidobacterium strains reduce the gut permeability to Shiga

toxins produced by *E. coli* O157:H7 strains (Fukuda et al. 2011).

(2) The second mechanism is the (immune system mediating mechanism) through the activation of the immune system to fight invading pathogens via: (A) The cell wall of fungi such as *Candida albicans* and yeast which contain active substances such as β -Glucan and mannan oligosaccharides (MOS). β -Glucan modulates the cellular immune response against *S. Typhimurium* by increasing TCD4+ and TCD8+ cells (Winarsih et al. 2019). The β -glucans, in addition, induce antimicrobial peptide expression as an additional mechanism against *Salmonella* invasion in animal experiments (Shao et al. 2016).

Meanwhile, MOS was found to inhibit the adhesion of pathogenic *E. coli* and *Salmonella* to the gut endothelium. The pathogen binding capacity of MOS also extends to protect against *Pseudomonas* spp., *Shigella* spp., and *Vibrio* spp.; therefore, MOS is used traditionally in poultry feed as an alternative to antibiotics to control enterobacteria. Mannan resembles the cell receptors to which the pathogens adhere. The presence of fungal mannan in the gut entraps the pathogens to attach to it instead of adhering to the gut mucosa. Following the colonization on MOS, the MOS particles get cleared from the GIT. MOS has in addition a modulatory effect on the immune system, which acts as a general adjuvant (Özpinar et al. 2012; Xu et al. 2017). Similarly, non-pathogenic *E. coli* counteracts *Salmonella typhimurium* infection by systemic induction of IgG (Zeng et al. 2016). *Lactobacillus reuteri* diminishes infections with *C. albicans* through the initiation of type 3 innate lymphoid cell expansion accompanied by the production of interleukin 22 (Zelante et al. 2013). Meanwhile, the segmented filamentous bacterium was shown to induce T helper 17 cell differentiation. Subsequently, they initiate the production of peptides with antimicrobial activity in response to *C. rodentium* infections meanwhile the segmented filamentous bacterium was shown to induce T helper 17 cell differentiation. Some microbiota stimulate the immune system to provide protection against pathogenic fungi, e.g., *B. thetaiotaomicron*, which initiates the transcriptional regulator HIF-1 α , to produce an antimicrobial peptide (known as LL-37), which protect against *Candida albicans* activity (Fan et al. 2015). (B) The microbiota are also essential for the production of splenic CD4+. They can induce both B and T cells, which protects the gastrointestinal tract against intestinal pathogens. The gut microbiota plays a decisive role in the differentiation of T cells into T helper cells Th1s, Th2s, Th17s, and T regulatory cells (Atarashi et al. 2011; Ivanov et al. 2009). Fibrolytic microbiota also helps in local mucosal immunity (IgA) by the activation of B cells by the SCFA, where the SCFA can epigenetically control their expression via the inhibition of histone deacetylases and enhancement of histone acetylation. Microbiota also aids in the regulation of the production of

other immunoglobulins (Kim et al. 2016; Ubeda et al. 2017). (C) The circulating foreign antigens and metabolites of microbiota alarm the immune system (Gorjifard and Goldszmid 2016; Trompette et al. 2014).

Future therapeutic approaches

The fact that various chronic serious diseases are directly/indirectly induced by dysbiosis and the disturbance of the balanced equilibrium in our microbiome microenvironment or due to the epimutations in our epigenome opened the door for the development of evolutionary therapeutic approaches through the reestablishment of the microbial equilibrium and to reverse the undesired epigenetic modulations, as will be discussed in the following section (Table 1).

- 1) Prebiotics, probiotics, postbiotics, synbiotics, and antibiotics

Probiotics are living microorganisms (e.g., *Bifidobacterium*, *Lactobacillus*, or *Saccharomyces*), which are supplied orally to improve health status by competing with gut pathogens and enhancing the mucosal barrier integrity of the gut (e.g., *Lactobacillus* vs *Salmonella*), supplying the body with essential vitamins (e.g., vit B complex), providing an anti-inflammatory effect (e.g., *Lactococcus lactis* and *F. prausnitzii*) or modulating the immune system (e.g., *Saccharomyces*) (LeBlanc et al. 2013; Vieira et al. 2013; Zelante et al. 2013).

While the Prebiotics are non-digestible food elements that can be selectively utilized by beneficial gut bacteria. The most commonly used prebiotics are plant-derived polysaccharides such as inulin, FOS (fructooligosaccharides), MOS (mannan oligosaccharides), GOS (galactooligosaccharides), and XOS (xylo-oligosaccharide). These polysaccharides are utilized by anaerobic gut microflora to produce SCFAs, which are a major source of energy to the gut epithelium, act as local anti-inflammatory, and lower intestinal pH which inhibits the growth of enterobacteria and *C. perfringens*. They increase mucin production, maintain microvilli, and activate the immune system (Desai et al. 2016; Gallo et al. 2016; Lennon et al. 2014; Wang et al. 2012).

Meanwhile, the term psychobiotics was used recently to describe certain pre/probiotics which have the potential to improve the neurological signs related to certain disorders such as autism, Alzheimer's, and Parkinson's (Doenya 2018; Sampson et al. 2016; Sarkar et al. 2016; Sharma et al. 2021; Skonieczna-Żydecka et al. 2018).

The expression postbiotics refers to food supplementation with metabolites of beneficial bacteria, such metabolites include multiple vitamins, amino acids, organic and short-chain fatty acids, certain neurotransmitters, and enzymes. Finally, synbiotic is a term used to describe the simultaneous

Table 1 Therapeutic approaches of microbiota

Approach	Examples
Microbial transplantation	Fecal, vaginal, skin microbial transplantation (e.g., faecal transplantation for the treatment of Crohn's diseases)
Probiotics & postbiotics	e.g., <i>Lactobacillus</i> against Salmonellosis, <i>Bacillus thuringiensis</i> , against <i>Clostridium difficile</i>
Elimination of antibiotic-resistant bacteria	e.g., <i>Enterococcus faecalis</i> against vancomycin-resistant enterococci and <i>Staphylococcus lugdunensis</i> against MRSA
Activation/modulation of immune system	e.g., cell wall of <i>Candida albicans</i> and yeast

administration of both pre- and probiotics at the same time to provide a synergetic effect (Schrezenmeir and de Vrese 2001).

In the veterinary sector, manipulation of the gut microbiome through the addition of antibiotics to poultry feed is known for decades in order to increase body weight gain. In addition to antibiotics, both pre- and probiotics were also used as a supplement in poultry feed in many countries. In pet clinics, *Lactobacillus* and *Saccharomyces boulardii* were prescribed for the treatment of dogs suffering from gastroenteritis and IBD, respectively (Sauter et al. 2006). Similarly, *Enterococcus faecium* SF68 was administered to increase the immune response in young puppies and treat enteritis in the kitten (Benyacoub et al. 2005; Czarnecki-Maulden et al. 2007). Similarly, dogs suffering from chronic enteropathies were given tylosin the improvement of diarrhea via the enhancement of the gut microflora *Enterococcus* species (Kilpinen et al. 2015; Suchodolski et al. 2009) or administration of rifaximin to improve the clinical signs of dogs with IBD [167,168]. Supplementation with the probiotic *B. longum* and *L. helveticus* or the prebiotic inulin could relieve anxiety and depression in humans (Banta et al. 2019; Foster and Neufeld 2013; Valles-Colomer et al. 2019). It has also been introduced as an alternative therapeutic concept or could be combined with traditional therapy for bovine mastitis (El-Sayed and Kamel 2021).

The re-establishment of a balanced gut microenvironment by pre/probiotics can therefore aid in the treatment of such psychological disorders. Food supplementation with both *L. helveticus* and *B. longum* helps to reduce anxiety (Messiaoudi et al. 2011).

a) Probiotics

Supplementation with certain living bacteria/yeast species in adequate amounts can improve health conditions in different ways, including the reestablishment of equilibrium in the gut ecosystem, competition with harmful bacteria in the gut and prevention of their colonization, changing the intestinal pH, or other environmental conditions making them unsuitable for pathogens, production of useful metabolites such as vitamins and SCFAs, stimulation and activation of the

immune system, e.g., by IgA production or the direct activation of white blood cells, finally via the repair of leaky gut and increase mucin production (Gallo et al. 2016; Grześkowiak et al. 2015). According to published data, probiotics could be used in the treatment of autoimmune arthritis (by *Streptococcus lacticus* and *Bacillus bulgaricus*) (Warden 1909), STEC *E. coli* O157: H7-infections (by *Bifidobacterium longum* subspecies *longum* (JCM 1217)) (Fukuda et al. 2011), ulcerative colitis (by *Streptococcus salivaris* (Miele et al. 2009), acute gastroenteritis and rotavirus diarrhea (by *Lactobacillus rhamnosus*) (Hempel et al. 2012), and to impact the mental health and life quality by the supplementation with butyrate-producing *Faecalibacterium* and *Coprococcus* (Wallace and Milev 2017). Certain probiotics (e.g., *A. muciniphila*) are provided to type 2 diabetics to improve their insulin resistance and decrease their body weight (Anhê et al. 2015; Depommier et al. 2019).

Bifidobacteria population in the gut was found to be negatively correlated with the amount of fat in the diet. The decrease in their population is linked to leaky gut phenomena and an increase in blood LPS levels. Therefore, *Bifidobacteria* can be used as a probiotic supplement to improve glucose tolerance and decrease blood LPS levels (Cani and Delzenne 2009; Ley 2010). Recently, the use of non-traditional probiotics like *Clostridia* clusters IV, XIVa and XVIII, and *Faecalibacterium prausnitzii* was investigated because of their potent anti-inflammatory effect which was attributed to the effect of their metabolites mainly butyrate (Furusawa et al. 2013; Qiu et al. 2013; Vieira et al. 2016). In a recent study, daily supplementation with a mixture of five *Bacillus* strains in addition to prebiotic fibers could increase the amounts of released SCFAs (acetate, butyrate, and propionate) with a decrease in produced ammonia in the colon (Duysburgh et al. 2019). SCFAs, particularly propionic acid, can regulate lipogenesis and cellular glucose intake via its role in upregulating the expression of the glucose transporter 4 (GLUT-4), lipoprotein lipase, and the sterol regulatory-element-binding protein (SREBP-1c) (Rezaee 2019).

The released SCFAs stimulate SCAF-specific receptors which regulate cellular energy intake and requirements (Morrison and Preston 2016; Ohira et al. 2017). In addition,

SCAFs can also stimulate niacin receptor 1 to exert anti-inflammatory, anti-carcinogenic, blood triglycerides/LDL-lowering effects (Singh et al. 2014).

b) Prebiotics

Prebiotics have become a future trend for the treatment of metabolic disorders in the last few years as they support the intestinal microflora and decrease intestinal permeability. They have proven positive effects on insulin resistance and body weight (Boutagy et al. 2016; Colantonio et al. 2019; Cox et al. 2017; Pedersen et al. 2016). Supplementation with undigested polysaccharides of plant origin is important for the enrichment of gut microbiota with *Lactobacillus* and *Bifidobacterium* which ferment them into SCFAs (Sims et al. 2014).

c) Postbiotics

The term postbiotic was recently created to describe the supplementation with non-viable heat-inactivated probiotics or bacterial byproducts/metabolites (e.g., organic acids and SCFAs) which possess biological activities (Patel and Denning 2013). This therapeutic concept depends on providing the hosts with biologically active substances without subjecting them to the risk of administering living organisms (Shapiro et al. 2014). Clinical trials which were carried out using SCFAs as postbiotics could reduce signs of inflammation in gout, pneumonia, arthritis, colitis, and asthma (Maslowski et al. 2009; Trompette et al. 2014; Vieira et al. 2016).

d) Synbiotics

Regular consumption of synbiotics improved cases of atopic dermatitis, hyperlipidemia, and gastrointestinal disorders (Farid et al. 2011; Fujimori et al. 2009; Shakeri et al. 2014).

e) Antibiotics

The microbiome is regularly exposed to a wide range of antibiotics either directly administered as medication or unintentionally as residues in foodstuffs. This permanent exposure leads to changes in the microbial composition, a rapid drop in microbial diversity in the gut, increases susceptibility to infectious diseases (mainly by *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Clostridium difficile*), and enhancement of fungal growth and promotes the evolution of antibiotic-resistant bacteria. This, in turn, promotes long-term metabolic, pathological, and epigenetic changes. Early exposure of infants to antibiotics may induce long-term diseases (e.g., obesity) which occur later in life (Francino 2016). Despite the wide range of side effects associated with

antibiotic therapy, none of the registered antibiotics was shown to have carcinogenic side effects. However, some reports linked the repeated use of macrolides with biliary tumors, or sulphonamides with breast cancer. The increased prevalence of cancer in patients receiving repeated courses of antibiotic therapy is attributed to the resulting dysbiosis because of long-term administration of antibiotics (Boursi et al. 2015).

However, several research teams investigated intentional manipulation of gut microbiota by the administration of antibiotics to induce microbial shift to treat certain disorders (e.g., the administration of metronidazole for the improvement of enteric signs in Crohn's disease patients via the enhancement of *Bifidobacterium* spp.) (Ambrose et al. 1985; Chlebowski et al. 2006; Igarashi et al. 2014; Scribano and Prantera 2013). The administration of metronidazole was also shown to reduce *Fusobacterium* load in gut microbiota which inhibited the proliferation of colon cancer cells and the overall tumor growth in animal experiments (Bullman 2020). These findings are supported by Schulz and his team (2014) who completely blocked the progression of high-fat diet-induced colorectal cancer via the administration of antibiotic mix (Schulz et al. 2014).

2) Through transplantation of microbiota:

Although microbiota transplantation is well known in the treatment of certain animal diseases such as cattle rumen acidosis, however, this approach is completely unfamiliar to humans. Recent studies have indicated the decisive role of the transplantation of fecal/gut microbiota from healthy donors to diseased persons. The great success and promising data delivered from these investigations in the treatment of inflammatory diseases, especially those induced by gut dysbiosis, encouraged further steps such as treatment via transplantation of vaginal microbiota (vaginal fluids) from healthy females to diseased ones. Even skin microbiota transplant was tried (Perin et al. 2018).

Fecal microbiota transplantation

In the last few years, fecal microbiota transplantation (FMT) became a new therapeutic approach. In this approach, fecal microbiota are transplanted from healthy individuals to diseased ones. However, this concept still faces many obstacles such as (1) the significant role of microbiota in disease induction/disease improvement, (2) not all members of the microbiome are identified, (3) trillions of viruses/fungi or protozoa are also present in the gut, (4) the exact role of most of these species in disease induction/prevention is not clear, (5) many disorders have multifactorial causes and occur due to the interaction among various members of the microbiome, and (6) many of the commensal bacteria may become

pathogenic by changing the micro-environmental circumstances. In addition, the implanted fecal materials contain, besides the viable microbiota, various metabolites, such as bile salts, vitamins, SCFAs, proteins, and hormone-like substances and surely various unknown substances (Choi and Cho 2016; Kang et al. 2017; Kootte et al. 2017a; Kootte et al. 2017b). The curative effect of FMT may be attributed to all these elements and not restricted to the direct effect of implanted microbiota alone. Therefore, supplementation with one or more species of bacteria/yeast as probiotics usually has limited therapeutic effects. Based on this, the transplantation of fecal material from healthy donors to the gut of disease recipients (known as FMT) was investigated as a promising therapeutic concept. Fecal material can be introduced orally via a nasogastric tube or rectal enema/colonoscopy (Brandt et al. 2012; Choi and Cho 2016; Gupta et al. 2016).

This therapeutic concept was supported by clinical trial to treat certain disorders which occurred following antibiotic therapy and were attributed to the disturbance of the microbial balance in the gut. Many of these disorders were again improved following the administration of probiotics (Gareau et al. 2008; Lurie et al. 2015; Odamaki et al. 2012; Pinto-Sanchez et al. 2017; Sevelsted et al. 2015).

Since the first trial in 1958, limited trials were carried out using fecal transplantation for the treatment of bowel inflammatory diseases such as irritable bowel disease (IBS) (Eiseman et al. 1958; Johnsen et al. 2018), ulcerative colitis (UC) (Cui et al. 2016), Crohn's disease (CD) (Bak et al. 2017; Magro et al. 2019) and even CD accompanied with epilepsy (He et al. 2017), *Clostridium difficile* infection infections or following antibiotic therapy for the treatment of antibiotic-induced diarrhea (Mattila et al. 2012; Van Nood et al. 2013). FMT could also improve the clinical picture of patients suffering from multiple sclerosis, and myoclonus dystonia (Angelberger et al. 2013; Borody et al. 2011; Grehan et al. 2010).

Recently, the therapeutic spectrum of the FMT technique was also extended to involve diseases like liver disease, blood disease, metabolic diseases (insulin resistance), and even neurological disorders such as Parkinson's disease and autism (Bajaj et al. 2017; Kakihana et al. 2016; Kang et al. 2017; Philips et al. 2017; Vrieze et al. 2012) and the clear improvement of the clinical picture in 80% of the cases treated by FMT in children suffering from autism spectrum disorders (ASDs) is not fully understood because autism is believed to be initiated by the interaction of various genetic/epigenetic factors and to less extent due to dysbiotic gut microbiota (Dominguez-Bello et al. 2010; Kang et al. 2017; Krajmalnik-Brown et al. 2015). However, animal experiments on mice suffering from autism-like syndrome showed that the lack of certain gut microbial inhabitants and their metabolites worsen the condition (Hsiao et al. 2013). Therefore, FMT therapy showed promising and safe therapeutic potency for

children suffering from autism (Kang et al. 2019; Zhang et al. 2018). Similarly, people who received gut microbiota from overweight persons developed later overweight, while those who received microbiota from lean persons lost their overweight (Alang and Kelly 2015).

a) Vaginal microbiome transplantation

Lactobacillus dominated the vaginal microbiota. The disturbance may lead to a higher risk of venereal diseases, urinary tract diseases, preterm birth, and genital tract cancers (DeLong et al. 2019). Recently, pro- and prebiotic products were developed to recover the vaginal health status via the reestablishment of the normal microbial equilibrium in the vagina (Al-Ghazzewi and Tester 2016). The reestablishment of vaginal microbial balance is also necessary for the improvement of fetus health later in life (Dominguez-Bello et al. 2016).

b) Skin microbiome transplantation

Skin is our first line of defense against diseases. Part of this role is already played by the normal skin inhabitants (skin microbiota), which colonize the skin surface at a density of one billion microorganisms per square centimeter. The skin microbiota contains various bacterial and fungal spp. which co-exist in a balanced ecosystem. Any disturbance of this ecosystem results in disease conditions. One of the major skin inhabitants is *Staphylococcus epidermidis* which plays a great role in skin protection against inflammations induced by UV exposure (Keshari et al. 2019). *Patients suffering from skin dysbiosis are well documented. This is usually accompanied by immune dysregulation and infections with Staph. aureus due to impaired skin barrier function. These conditions, commonly known as atopic dermatitis, could be improved in animal experiments by the colonization of gram-negative skin bacteria particularly Roseomonas mucosa. The application of the achieved results on human patients suffering from the disease improved their skin condition* (Myles et al. 2018).

3) Therapeutic concepts via epigenetic modulations

Due to the reversible nature of epigenetic aberrations, it could be possible to reverse the pathological lesions/disorders resulting from epigenetic modulations (Jones and Baylin 2002, 2007). Epigenetic-based drugs can act through various epigenetic modulatory mechanisms such as methylation inhibition (e.g., zebularine which has a dual work mechanism by (1) inhibition of DNA methylation and in the same time activating the silenced genes) (Cheng et al. 2003) or antisense oligonucleotides (Amato 2007), (2) chromatin modification by bromodomain (acting on acetylated lysine residues) (Dawson et al. 2012), (3) histone acetylase (HAT) inhibitors which downregulate gene expression and enhance

apoptosis (Morimoto et al. 2008; Santer et al. 2011), (4) protein methyltransferase (PMTs) inhibitors (Copeland et al. 2009; Fu et al. 2014), (5) histone deacetylases (HDAC) inhibitors (Sarkar et al. 2013), (6) modified microRNAs (miRNAs) to mimic the tumor-suppressive miRNAs miR-34 and miR-16 molecules (Slaby et al. 2017), and for the treatment of Hepatitis C viral infections (Janssen et al. 2013; Ottosen et al. 2015).

At the time, many trials have been carried out to treat cancer based on the epigenetic reestablishment of healthy epigenetic profiles. These trials depend on the activation of cell apoptosis and stoppage of uncontrolled cell division through the reactivation of tumor gene suppressors (Griffiths and Gore 2008). Promising results for the treatment of ovarian cancer were obtained following the suppression of hypermethylated *OPCML*, *BRCA1*, *p16*, and *TMS1* genes (Makarla et al. 2005; Teodoridis et al. 2005; Verma and Kumar 2018). Other epigenetic-based drugs were also successfully applied against liver, pancreatic, and breast cancer (Li et al. 2015a; Zhou et al. 2014) and for the treatment of gastric and lung cancer (Karthik et al. 2014; Zhou et al. 2014).

Similar concepts are now under investigation for the treatment of non-infectious chronic diseases such as Alzheimer's disease and hypercholesterolemia and atherosclerosis (Byrne et al. 2014; Cacabelos and Teijido 2018; Fitzgerald et al. 2014; Rotllan et al. 2013; Sharma et al. 2021).

4) Forest, green and blue therapy

The modern civilization and the lifestyle in overcrowded cities are usually closely associated with noise, stress, and artificial light in the evening. The reduction in green areas is automatically reflected in the form of lower oxygen concentration and higher pollution rates (Kumar et al. 2019), investigating the therapeutic impact of forest therapy revealed its significant improvement of both psychological and physical health status. It enhances body defenses against infectious agents via the improvement of immune competence mainly through the increase in NK efficiency. It significantly improves the quality of life and relieves chronic widespread pain, depression, anxiety, and emotional disorders (Han et al. 2016).

It can also improve the situation of patients suffering from non-infectious diseases such as cardiovascular diseases (including hypertension and stroke), metabolic diseases (as diabetes mellitus and obesity), respiratory diseases (as asthma), and cancer (Bielinis et al. 2019; Han et al. 2016; Kumar et al. 2019; Li et al. 2021). Additional positive impacts of forest therapy included anti-inflammatory and anti-allergic effects (Andersen, 2021 #3526, Paciência et al. 2021).

In conclusion

As the microbiota can play a major role in the progression and suppression of several epigenetic diseases, the maintenance of a balanced microbiome provides a novel therapeutic approach for several serious diseases. In the last decade, extremely valuable data were gained regarding the role of epigenetic modulations in the induction of diseases, the role of the microbiome, and the exact mechanisms of interaction among them in disease pathogenesis. The reversible nature of epigenetic modulations in contrast to genome mutations, and the ease of manipulation of our microbiome through changing diet and lifestyle patterns or through the supplementation with pre, pro, or probiotics or through microbiome transplantation open the door to develop safe and efficient therapeutic approaches for serious chronic diseases such as cancer or autism. At present, studies investigating the efficiency of additional natural therapeutic approaches of alternative medicine such as forest therapy and green/blue spaces for the treatment of several somatic and psychological disorders continue to deliver promising data and may replace traditional medication in the near future.

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