# Association of human microbiome with health and disease states

Hanan A. Al-Ashaal

Chemistry of Natural Compounds Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Giza, Egypt

Correspondence to Hanan Abd Al-Hay Saied Al-Ashaal, PhD, Pharmaceutical and Drug Industries Research Division, National Research Centre, 33-El-Bohouth Street (former El Tahrir Street) PO Box 12622, Dokki, Giza, Egypt. Tel: +20 111 115 2820; fax: (+202)33370931; e-mail: hanan_alashaal@yahoo.com

**Received** 5 December 2018
**Accepted** 27 February 2019

**Egyptian Pharmaceutical Journal** 2019, 18:75–87

This review deals with microorganisms that are associated with the human body, their types and diversity. The survey also covers the symbiotic and adverse effects of the located flora and how could friendly microbial communities change to vigorous pathogenic enemies. Besides, the study includes special oversight on the natural compounds that may help to overcome serious diseases that are caused by or that result from microbiome alteration or dysbiosis.

**Keywords:**
commensals, dysbiosis, microbiome, natural remedy, pathogens, symbiotic

Egypt Pharmaceut J 18:75–87

1687-4315

## Introduction

The human body is covered with microbial flora in balance that exerts no harm to human beings. Really, it could be regarded as human's own well-organized ecosystem against attacking harmful pathogens [1]. There are trillions of microorganisms living in and on the human body including the skin, mouth, and gut having a crucial role in human health and disease states [2].

The term 'microbiota' refers to the different microorganisms that are associated with the human body on the inside and the outside. Similarly, 'microbiome' is the catalog or bibliography of these microorganisms and their gene maps. Microbiome could also be defined as the genetic materials of all microbes that exist on the outside and inside of the human body including bacteria, fungi, Protista protozoa, and viruses [3].

The terms microbiota and microbiome are usually used interchangeably [4]. Meanwhile, metagenomics is the total DNA characterization of the genomic analysis of the microbial community, now it is applied to genetic marker studies [4]. The microbiome encodes nearly100–200-fold more genes than that of the human genome [3,5].

Regarding biomass and diversity at the human gut and associated locations, bacteria cover the vast majority of human microbiota that resides within the host. Other microorganisms such as archaea, viruses, and eukaryotes including yeast and protozoans are also represented in the gastrointestinal tract (GIT) and in other body sites but to a lesser extent [6–8].

It is interesting to know that the microbiota that a new born starts to gain, is based highly on the delivery way. Few minutes just after a baby is born, vaginal born infant's microbiota looks like that of his mother's vaginal microorganisms, whereas infants born by cesarean harbor microbial flora that exactly exist on adult body skin [9,10].

The composition of the microbiome is greatly dynamic at the first 3 years of life after that it becomes relatively steady and more adult-like. However, many smaller changes continuously occur during childhood, adolescence, middle age, and old age [11–15]. In spite of the preponderance of the microbial cells in the human body, they have small, mitochondria-like dimensions and all account for only several pounds of human body weight, corresponding to 2–7% of each person's biomass, excluding water weight [5].

There are intervariations and intravariations in the human microbiome community and its role according to human body habitat, host location, age, sex, race, and nutrition [4,16]. The distinction of each individual's microbiome community appears to be steady over time specifically the microbiome associated with health [17].

Even healthy persons vary remarkably in their microbial community and abundance in different habitats such as the gut, skin, oral cavity, and the



 DOI: 10.4103/epj.epj_46_18

vagina. Signature genera interdiversity occurs within the habitats of the same individual such as *Prevotella amnii* in the vaginal habitat and *Prevotella copri* in the gut habitat or intradiversity between individuals as in the case of vaginal *Lactobacillus* spp. [17].

In the case study, *Staphylococcus aureus*, on the skin exhibited 29% nasal carriage rates and 4% skin rate [18]. Similarly, phylogenetic relatives such as commensal *Staphylococcus epidermidis* spread on the skin and existent in 93% of nare specimens [17].

## Association of human microbiome with health

Symbiotic bacteria associate with the host directly after birth and gradually colonized development takes place into a highly multiple ecosystem along with host growth [19].

Microbiome within and among human body habitats including the gut display proposed relationships to dominate the health physiological process such as driving physical agents such as oxygen, moisture, host immune factors, and microbial influence such as mutualism or opposition [17].

Human microbiome includes far more adaptable metabolic genes exceedingly those of human genes, and supplies humans with particular enzyme-mediated biochemical paths. Microbiome enhances both food energy extraction and nutrient harvest [20–22].

In addition, the human microbiome acts as a physical barrier and protects the host against the invading pathogens via competitive exclusion and antimicrobial production [23–25].

Similarly, the microbiota is vital in the intestinal mucosa and immune system development of the host [26,27].

Commensal intestinal bacteria is implicated in the digestion of indigestible foods by stomach and small intestine, and plays an important role in energy balance. Primarily dietary vegetable fibers such as xyloglucans could be digested by certain species of *Bacteroides* [28]. Fructo-oligosaccharides and oligosaccharides are also nondigestible fibers that can be utilized by symbiotic microbes, such as *Lactobacillus* spp. and *Bifidobacterium* spp. [29].

Gut microbiome is associated with essential vital biological processes such as metabolism, immunity, and controlling epithelial growth [2].

Besides, gut microbiota have an essential role in lipid and protein balance and in the microbial biosynthesis of basic nutrient vitamins such as vitamins K and B.

The commensal gut microbiome produces short-chain fatty acids (SCFAs) like propionic and butyric, thus providing energy supply to the intestine. SCFAs physiologically affect blood flow to colon mucous membrane, fluids and electrolyte absorption. SCFAs also influence the autonomic nervous system and the gut hormone secretion [30].

These SCFAs could be rapidly absorbed into the host colon and are associated in adjusting the gut motion, inflammation, glucose balance, and energy consumption [31,32].

In addition to gut bacteria, enteric viruses could also enhance the normal development of the mucosal immune system [33].

Regarding skin, it is a mediator with outer milieu and so is also colonized with multi aggregates of microorganisms such as bacteria and fungi microbes in addition to viruses and mites [34].

One of the most beneficial aspects of skin commensals is the physical barrier they offer, prohibiting colonizing of other more pathogenic bacteria [35]. Skin microbiome could interact with harmful pathogens and locally modulate the immune system [35]. The two utmost dominant bacteria that inhibit the skin are *S. epidermidis* (Gram-positive coccus) colonizing the epidermis and the *Propionibacterium acnes* (Gram-positive rod) colonizing the adipose glands [36].

These two bacteria endure aerobic and anaerobic media, even though *P. acnes* only develop well under microaerophilic or anaerobic status [37]. The sebaceous glands are generally solely colonized by *P. acnes*. One reason of such singular colonization could be the capacity of *P. acnes* for propionic acid production through carbohydrate fermentation.

Although *P. acnes* is capable of bearing local pH reduction in sebaceous glands, other bacteria could not tolerate that environment. As an example, in a skin infection model, *S. aureus* which is a skin pathogen could be killed by the produced propionic acid biosynthesized by *P. acnes in vitro* as well as *in vivo* due to the internal pH reduction mediated by increased propionic acid concentration [38]. Furthermore, *P. acnes* has also been documented to carry genes

coding to produce bacteriocins antimicrobial proteins as well as and antimicrobial peptides (AMPs) [39].

Not all commensal bacteria could solely produce the antimicrobial proteins and the AMPs, but can to some extent process human AMPs to direct the skin immune system. Similarly, *S. epidermidis* could produce an enormous array of antimicrobial bacteriocins that are effective against *S. aureus* and *Streptococcus pyogenes* which are skin pathogens [40].

Because of their commensal nature that has been directed toward its immune modulator role, and as director for proper immune system, *S. epidermidis* also influences the local skin immunity to generate an efficient local immune response versus pathogens such as *Candida albicans* [41].

Numerous food supplements that include probiotic ingredients are now produced by the pharmaceutical companies to support the normal functioning of body systems. Besides, there is also local preparations that contain prebiotic that promotes specific healthy strains of bacteria to develop.

## Factors that influence microbiota alteration

The occasional pathogenicity of these commensal bacteria is not well known. However, majority of these symbiotic bacteria could be referred as opportunistic microbial pathogens, being capable of causing disease once a chance or 'opportunity' is found; this chance may be impaired immunity, unregulated microbiome, immunological barriers, breaches or bacteria localization changes, and last but not the least antibiotic intake. These opportunities are among the factors that contribute to many important infections and trigger the pathogenicity of the microbiota [35].

### Antibiotics: irrational use

Gut microbiota once established is quiet stable over time. However, there are a number of reports that clarified that there are exterior forces that can change the microbial combination present in GIT; antibiotics are famous examples [4].

Antibiotics are fundamentally used to fight pathogenic bacteria that have invaded the host; but the kind of antibiotics that are available now are mainly vast spectrum and affect a wide range of normal flora likewise.

The occurrence of antibiotic-resistant infections is increasingly elevated; meanwhile the new antibiotics discovery rate is slowing. In addition to resistance development, the use of antibiotics strongly disturbs the ecology of the human microbiota [42].

Thus, antibiotics significantly influence the host's natural gut microbiota. As an example, few days after ciprofloxacin antibiotic treatment, the gut microbiota showed a reduction in taxonomic richness, variety, and equilibrium [43].

Mounting proof demonstrates that antibiotics affect the immune system function, human capability to resist infection, and the capacity for food processing [42].

A dysbiotic microbiota may not display vital functions such as nutrient supply, production of vitamins, and defense against pathogens such as the commensal community associated with many human physiological processes, and share in controlling immunity and metabolic balance [3,44].

Re-establishment of some bacterial species following antibiotic treatment can get up to 4 years and some species fail to return back to their community [45,46].

Hence, antibiotic intake could alter the essential physiological equilibrium, enhancing long-term maladies.

Besides, exaggerated antibiotic use promotes resistance to bacteria, thus the human microbiota turns to a significant reservoir for resistance genome, sharing the mounting difficulty in dominating infectious diseases. Broad-spectrum antibiotics can influence 30% of the gut bacteria, leading to a vast and significant decrease in taxonomic richness, variation, and balance.

Infants' microbiota could be altered in the same way by early antibiotic exposure. Antibiotics also influence gene expression, protein activity, and overall gut microbiota metabolism. These alterations could happen at a much quicker speed than changes comprising substitution of the flora [44].

Enhanced capability to intestinal infection is one of the most significant threats associated with gut microbiome disturbances, which can emerge from foreign pathogens or from unexpected overgrowth with pathogenic performance of already present opportunistic microorganisms within the microbiome.

The microbiome dysbiosis caused by antibiotics, in addition to increasing immediate infection risk, could also affect essential immune balance with

body-wide and long-term consequences. Gut microbiota dysbiosis has been linked to atopic, inflammatory, and autoimmune syndromes, and, in certain cases, remarkable association has been confirmed between these diseases and administration of antibiotics during early childhood, a decisive period for the maturation of the immune system and immunological tolerance fixation [44].

#### Bacterial dislocation

The equilibrium in the microbiota is very essential for the human body's health that builds on the strict control of interaction between the microbiota and humans. Microorganisms or microorganism components translocation, from the GIT lumen to systemic circulation obviously exhibit detrimental results, as an enhancement of body immune system.

Severe states of microorganisms' translocation may lead to septic shock, where death can reach 70% of patients and is distinguished by clinical symptoms such as thermal irregularity including hypothermia or hyperthermia, tachycardia, and alteration of white blood cell counts [47]. Similarly, as a result of bacterial translocation, there is massive induction of inflammatory cytokines including tumor necrosis factor, interleukin, and high motility group 1 protein and nitric oxide. In spite of that inflammatory response could be beneficial to limit the infection and hazards of the tissue; their exaggerated production induces high systemic inflammatory responses which may lead to lethal results more than the infection of bacteria itself [48].

Significance of such a phenomenon is of important relevance in acute sepsis, because extreme production of proinflammatory mediators results in capillary infiltration, injury of the tissue, in addition to multiple organ disability [48].

The proinflammatory mediators are mainly produced by natural immune cells poststimulation via specific bacterial product receptors. Thus, protecting against excessive microbiota translocation may be considered as essential to life.

Recently, both *P. acnes* and *S. epidermidis*, the commensal bacteria, are debated as opportunistic pathogenic microbes because of their incorporation into medical implantation, especially venous catheters and joint implantation [49,50]. It has been confirmed that these skin mutual commensals could exert low-grade localized inflammation, often chronic, upon attachment to medical implantation [51]. Less commonly, infections caused by these symbioses could occur in the absence of medical implants, including endocarditis [52].

## Autodefense approaches against microbiome translocation

#### Gastrointestinal surface defense

First defense line versus microbiome translocation is mediated by macromolecules in the GIT lumen, including mucus layer constituents such as phospholipids, lumen electrolytes, and proteins, in addition to water.

The gel-forming properties of mucus glycoprotein could also participate in the protection of the underlying epithelial tissues. Moreover, luminal immunoglobulin (Ig) A and antimicrobial defensins produced by the GIT epithelial cells (Paneth cells) could bind to and kill the bacteria, thus restricting their ability of translocation. Hence, the GIT epithelial barrier represents a significant difficulty against microbiome translocation [53].

#### Liver defense

Clearance of external and potentially harmful materials which drain through the GIT is one of the many important functions performed by the liver. Liver contains cells other than parenchymal hepatocytes including liver sinusoidal endothelial cells (LSECs) which constitute the liver sinusoidal wall, tissue macrophages (Kupffer cells) that are located mostly in the periportal area and liver-associated lymphocytes [54].

So, Kupffer cells are quite situated for the phagocytosis of antigens and organisms in venous circulation. Both Kupffer cells and LSECs response directly to bacterial products stimulation, with pronounced responses compared with other tissue macrophages and monocytes in the circulating blood [55].

#### Systemic circulation defense

In case that microbes and microbial products escape the GIT lamina, macrophages uptake and escape liver clearance via LSECs and Kupffer liver sinusoids; once this happens, in the circulation, microbial products are faced with additional host-mediated reactions controlled by cell receptors which sense and circulating factors bind to and scavenge these microbial products.

Healthy human beings have high titers of circulating Ig antibodies, IgM, IgA, and IgG that are directed

toward these microbial products and neutralize their activity [56,57]. Furthermore, the natural immune system enhances the soluble circulating protein factor production by peripheral blood monocytes and tissue macrophages following microbial products' stimulation and binds to them [58,59]. These factors act as basic lines of defense versus systemic immune system stimulation by microbial translocation of antigens.

## Association of human microbiomes with diseases

As the balanced microbiome dominates healthy process, dysbiotic microbiome has been implicated in many diseases. This dysbiosis could be recognized in obesity, type II diabetes, eczema, celiac disease, cancer, psychiatric disorders, asthma, inflammatory bowel disease (IBD), and chronic diarrhea [47].

In certain cases, it is difficult to deduce that an altered microbiota is disease causative or dysbiosis is a result of the disease that affects the microbiota composition. With respect to newly born infants, geographical location, mother breastfeeding, way of birth, and antibiotic administration are all factors that can clearly alter the microbiota composition, thus, in this case, microbiota alterations that are noticed in disease circumstances could be a sequence rather than disease cause [60]. Relative reports of culturable microbiota of HIV patients have shown significant differences between uninfected and infected individuals, proposing that the microbiota alteration might contribute to the progression of HIV disease [61].

### Human microbiome and infectious maladies

Infection is widespread of diseases induced by impaired microbiota, following translocation of intestinal bacteria. Harmful pathogens colonize intestinal mucosa leading to induction of strong inflammatory response [47,62]. Importantly, infectious diseases and their treatments including antibiotics, immunosuppressive drugs, exhibited a strong influence on body microbiota that in turn defines the effects of these infectious diseases to the infected person. The microbiota disorder is also associated with the development of virus infections [2].

### Inflammatory bowel disease

Alteration of the GIT microbiota composition has been indicated to have a role in the pathogenesis of IBD, as illustrated by mouse modeling of IBD where a significant reduction of inflammation was achieved upon housing the mice in germ-free conditions [47,63].

Persons with IBD also display increased amounts of circulating proinflammatory mediators and, due to microbiota translocation, have been proposed to be the cause of this systemic inflammation [47].

### HIV infection

At the present time, HIV infection still is a main global public health problem. Microbiomes in the GIT of infected persons having HIV are markedly impaired, and the ratio of Firmicutes to Bacteroidetes is significantly elevated in infected patients [64]. Although the viral burden of HIV-1 is diminished after short-term course of efficient highly effective anti-retroviral treatment, microbiota variety and composition are not completely repaired, and the alteration remains [64].

Recently, reports have illustrated that the vaginal microbiome could affect HIV infection risk. *Prevotella bivia* which is a vaginal bacterium has been identified as the inflammation causing bacterium. Unusual bacterium called *Gardnerella* spp. was found in the vagina of South African women and girls, explaining the high infection rates in South Africa [65].

### The human microbiome and liver aliments

Considerable evidence illustrated liver and GIT interaction and chronic liver exposure to gut-derived factors such as bacteria and bacterial components, fostering the gut–liver axis term [66].

Liver function is affected by the intestinal microbiota which produces microbial products such as ethanol, ammonia, and acetaldehyde that are metabolized by the liver and dominate Kupffer activity and production of cytokinins through endotoxin release [67].

Intestinal microbiota alterations have an important role in promoting liver damage induction and progression through different mechanisms such as stimulation of Kupffer liver cells by the released bacterial endotoxin [68]. Gut microbiota shares in liver cirrhosis pathogenesis, involvements such as infections, peritonitis, liver encephalopathy, and kidney failure. People having cirrhotic liver disease show dysbiotic gut bacterial components [69].

Cirrhotic patients show an increase in the number of species of *Proteobacteria* and *Fusobacteria* and a decrease in the number of Bacteroidetes spp. [70]. In line with the previous study, following the metagenomics technique, *Bacteroides* spp. was found to be reduced at the genus level. Moreover, *Veillonella* spp.,

*Streptococcus* spp., and *Clostridium* spp. are enriched in cirrhotic patients [71]. Impaired duodenal mucosal microbiota was also recognized with liver cirrhosis patients [2].

Likewise, liver is influenced by the oral microbiota. Oral microbiome is one of the most important microbiota in humans. Duodenum dysbiosis might be associated with oral microbiota alterations [72]. Oral microbiome diversity and composition of patients having cirrhotic liver, significantly varied from healthy individual's microbiome and from microbiome of patients having hepatitis B virus-related chronic ailments. Harmful bacteria could be inhibited in and come from oral cavity. Besides, patients with chronic liver maladies display oral disorders [73].

Impaired gut microbiota is recognized in patients with acute-on-chronic liver failure syndrome (ACLF). It is reported that there is a link between certain bacterial genera and inflammatory cytokines release in ACLF patients. This indicates that gut dysbiosis is correlated to the mortality of patients having ACLF [74].

The changes in liver cirrhosis are directly relayed to dimensioned intestinal motion and pancreatic secretion, intestinal barrier disturbances, and reduced gastric acidity. In addition, most of hepatocellular carcinoma grow in a medium of chronic injury, inflammation, or hepatic fibrosis [75].

Alterations of the gut microbiome enhance hepatocellular carcinoma cross participating to hepatic inflammation via enhanced intestinal permeability. Moreover, gut taxa are relevant to the pathogenesis of autoimmune liver diseases. Liver diseases are generally connected with enhancement in Enterobacteriaceae with a reduction in *Bifidobacterium* spp. Gut dysbiosis could result in endotoxemia in patients via bacterial translocation. Endotoxemia may cause immune dysfunction, resulting in the necrosis of liver cells and liver failure [76]. Patients with autoimmune liver diseases show distinct gut microbiome and significant increase of *Escherichia* spp., Lachnospiraceae spp., and *Megasphaera* spp. bacterial abundance, with near absence of *Bacteroides* spp. [76].

#### Bacterial vaginosis

Bacterial vaginosis is regarded as an alteration of the vaginal microbiota. Vaginal dysbiosis is linked with a lot of virulent health consequences such as preterm neonatal and exposure to sexually transmitted diseases [2].

#### Cancer and associated microbiomes

Microbial pathogens are the causative agents for 15–20% of cancer cases, but commensal microbiome has a more widespread effect on the initiation and development of tumorigenesis. Metagenomic studies have disclosed significant variations in the composition of the microbial community in many human malignancy cases compared with normal [77,78]. The main conclusion arising from these studies is that carcinomas are associated with microbiota dysbiosis that includes a marked reduction in both microbial diversity and community stability. Microbiome variations differ on a case-by-case basis and generally comprise comparatively modest quantitative variations in the abundance of certain species of bacteria [5,77,78].

Optimistically, the processes of microbial pathogenesis supply possible routes for malignancy diagnosis and handling. Retrieve eubiosis in chronic illness might improve carcinogenic hazards [79].

#### Gastric carcinoma

The commensal microbes in the GIT have a remarkable role on cancer development which arises within the GIT. Modern advances regarding microbial studies on gastrointestinal malignancies highlight the role of the human microbiome in tumorigenesis of gastric carcinoma [2].

Gut dysbiosis mainly involves alteration in the abundance of commensal bacteria, including some opportunistic pathogens. Although *Helicobacter pylori* infection is the most predominant risk factor in gastric cancer, gastric colonization by other bacteria (non-*H. pylori*), many of which also colonize the intestine and could impact the risk for gastric cancer [80].

#### Colorectal carcinoma

Microbial alteration is involved in the development of colorectal benign adenoma and cancer (colorectal cancer). Pathological imbalance in the microbiome community is spotted in individuals having adenomas compared with healthy ones [81,82]. But it remains indistinct from reported studies if alterations of the microbiome community are caused or results from adenoma and colorectal cancer.

Significant increment in *Bacteroides* spp. and *Echerichia coli* in addition to periodontal pathogen (*Fusobacterium nucleatum*) have been observed in alteration from advanced benign colorectal adenoma to carcinoma [83,84]. DNA damage may be induced by *Enterococcus faecalis* and *E. coli* by promoting the

release of extracellular free radical superoxide in host cells [85].

In spite that these remarks illustrate etiological association of intestinal microbiome in colorectal carcinoma, further research still is required to define their suggested role as colorectal carcinoma markers or their use as diagnostic or curative targets. In addition, plenty of bacterial-derived byproducts are incorporated in repression of colon tumor growth. Such metabolites that are produced by microbial biofermentation of polysaccharides include acetate salts, propionate as well as butyrate salts that serve as energy sources for colonic epithelial cells.

Butyrate has been found to protect against colonic neoplasia. It is reported that a high fiber-containing diet leads to a reducing risk of initiation of colon cancer on account of butyrate salts production [86,87]. In in-vitro research of cancer cell lines, butyrate was reported to induce in-vitro tumor-repressing leverage through exerting apoptosis, suppressing propagation [88]. Thus, modulating gut microbiome via dietary control or antibiotic remedy could offer important therapeutic possibility.

Manipulating gut microbiome to stimulate production of these metabolites via feeding of indigestible food components may be a hopeful approach to dominate body metabolism, and so affect carcinogenesis risk [2].

#### Esophageal carcinoma

Frequent antibiotic treatment may result in long-term changes in esophageal microecology leading to an increasing morbidity from esophageal adenocarcinoma [2].

#### Breast cancer

It has been suggested that the gut microbiota contributes to breast carcinogenesis through translocation of gut microbiome to breast tissues. In addition to modulating the host immune system, gut microbiota could exert modification of systemic estrogen levels. Recently, there are reports that have proposed that breast tissue with cancer is connected with microbiomic description distinguished from benign normal breast tissue microbiota. Similarly, in breast cancers, microbiota of far distant sites such as oral cavity and the urinary tract display microbiomic conversion [5].

Cancer patients displayed a decrease in the relative abundance of *Methylobacterium* spp. and in contrast, increased abundance of Gram-positive organisms including *Corynebacterium* spp., *Staphylococcus* spp., *Actinomyces* spp., and Propionibacteriaceae spp. was recorded [5].

#### Pancreatic cancer

Pancreatic cancer has been known as inflammation-driven cancer, and there is essential preclinical and clinical evidence suggesting bacteria are being likely to affect the inflammation via stimulating immune receptors and through carcinogenesis-associated inflammation perpetuation.

Recently, many reports related to body microbiota have emphasized how disruption of the symbiotic bacterial community could enhance inflammation and enhance aliment processes, such as carcinogenesis. Association of inflammation with microbiome in pancreatic carcinogenesis could supply new targets for the involvement to prohibit and handle pancreatic carcinoma effectively [89].

#### Oral carcinomas

Human oral microbiome includes more than 1000 different microbes, such as bacteria and archaea in addition to viruses and eukaryotes. *Streptococci* spp. are the predominant bacteria, generally joined with *Veillonella* spp., *Gemella* spp., and *Rothia* spp. besides *Fusobacterium* spp. and *Neisseria* spp.

Normal stable oral microbiome cohabits with the human host. Upon dysbiosis, initiated by *Porphyromonas gingivalis* bacteria and *Fusobacterium* nucleatum, pathology could emerge, as periodontal malady or even cancer. Particularly, *Porphyromonas* spp. is enhanced at the surface of oral squamous cell carcinoma (OSCCs), and is also associated with disruption of immune response [79,90–92].

The oral cavity is heavily inhabited with microbial community having the biggest core of ordinarily participated microbes between different persons [93]. Environmental changes could enhance the potential for pathogenicity and support for oral diseases emerge [94]. Unique microbes inhibit the oropharynx including *S. pyogenes* and the pathogenic *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Haemophilus parainfluenzae* [95].

Doctors and dentists have explored the theory of focal infections in causing oral diseases which could potentially affect the far structures. One of the heavily discussed relations of periodontal disease and systemic conditions comprise cardiovascular aliments,

adverse gestation outcomes, diabetes mellitus syndrome, and respiratory maladies [96].

Correlation between oral aliments and systemic status promotes the relation of the effect of oral dysbiosis and oral cancers emerge.

Recently, reports have illustrated that periodontitis is connected with high risk of oral premalignancy development, eventually resulting in head and neck squamous cell carcinoma (HNSCC), basically OSCC in addition to oropharyngeal squamous cell carcinoma [97–100]. It was reported that patients having chronic periodontal inflammation usually have weakly differentiated HNSCC tumors at their oral cavity because of chronic inflammation [97]. Moreover, there is a synergetic relation between chronic periodontal inflammation and infection with oral human papilloma virus [101]. The periodontal pocket comprises squamous epithelial cells and is subject to reproduction constantly, transmigration, rete-ridge figuration and ulcer initiation, supplying chance for infection with human papilloma virus [101].

Salivary microbiome has been reported to influence patients suffering from Fanconi anemia (FA) regarding oral health condition and OSCC hazards [102]. FA persons are more susceptible to HNSCC growth compared with healthy persons [103].

The salivary microbiota of FA persons who are at increasing risk hazards of HNSCC development display a comparable variety profile as those non-FA persons having oral leukoplakia and OSCC. On the basis of these outputs, it was proposed that environmental agents including local microbiome, apart from ordinary risk factors could exert a role in enhancing OSCC in FA persons besides inherent genetic instability [103].

In a reported case study, oral microbiome displayed a significant role in esophageal squamous cell carcinoma. The results of this report further exemplify the possible risk linked oral microbiome changes with growth of nonbenign tumors [93].

#### Metabolic disorders

Two main metabolic disorders could be greatly affected by microbiome disturbance or dysbiosis which are obesity and type 2 diabetes mellitus.

#### Obesity

Host obesity was recognized with overgrowth of Firmicutes that changes the metabolic capability of the gut microbiota, inducing an increased capability of carbohydrate transfer leading to fatness [20].

Increasing studies illustrate that microbiota organisms that inhabit the gut are an important controller of the reaction between food and metabolic disease initiation [104]. Further, recent researches have shown that gut microbiota affects the biological clock that might subject to oscillations [105]. Disturbance of the host biological clock causes dysbiosis that is linked with body metabolic aliments [106].

Fatness, which is connected with gut microbiome dysbiosis and metabolic routes alteration, results in impairment of the gut epithelial barrier job and display critical impact to the physiological process like gut and immunity balance, energy consumption and metabolism, in addition to acetate and bile acid metabolism and, finally, release of the intestinal hormones [107–112].

#### Diabetes

Type 2 diabetes is a predominant metabolic aliment worldwide. The relation of dysbiotic microbiota and the progress of type 2 diabetes is progressively being discovered and the extent to which microbiota abnormality reached was correlated with plasma concentrations of glucose [113,114].

Increasing numbers of researches referred that alteration of gut microbiota, characterized by lower diversity and elasticity, is connected with diabetes. Induction of diabetes may be associated with the transmission of microbiome from the gut to tissues, leading to inflammation [115].

Laterally, it was reported that the human gut microbiome may induce resistance to insulin by microbial species like *P. copri* and *Bacteroides vulgatus* [116]. Gut microbiome may directly affect type 2 diabetes via affecting amino acid metabolism; hence, upcoming antidiabetic remedy strategy may target bacteria strains that induce imbalances in amino acid metabolism [114,117].

The association between periodontal diseases and diabetes is one of the most heavily debated relationships [93]. Latterly, interventions with microbiota to restore the balance of the gut microbiota have emerged. This approach includes the intake of certain fibers or therapeutic microorganisms. These approaches are hopeful programs to decrease resistance to insulin and associated metabolic disorders [2].

#### Asthma and allergic sickness

The way, place of delivery, and infant nutrition in addition to antibiotic administration in childhood, all affect gut microbiota diversity and composition and thereafter influence the risk of atopic manifestations and stimulate susceptibility to allergic asthma. It was reported that infants aged 3–6 months with a gut microbiome enriched with Clostridia and Firmicutes are associated with allergy to cow's milk at 8 years old. Early-life infant gut microbiome components could be one of the main determinants for cow's milk allergy consequences. In babyhood, specific members of the microbiome, such as *Clostridium* spp. regulate IgE l concentrations [118].

#### Microbiome and psychiatric syndromes

Recently, reports have emerged focusing on microbiome dysbiosis and the influence on different central nervous system disorders, including, anxiety, depression, schizophrenia, and autism [119–122].

Gut–brain axis is recognized since decades. This axis displays a main role in stabilizing regular brain and gastrointestinal functions. Latterly, the gut microbiome arises as a crucial controller of this axis. Microbiome–gut–brain axis is found to cover a number of systems, including endocrine and neural systems, in addition to metabolic and immune systems; all are involved in steady interaction [123].

Dysbiosis of the gut microbiome might enhance the transmission of gut bacteria through the intestine to the mesenteric lymphoid tissues, thus exciting immune responses which may lead to inflammatory cytokines discharge and the activation of the vagus nerve as well as stimulation of the spinal afferent neurons [124].

Autism aliment is documented to be connected with a modified gut microbiome, with a decrease in the mucolytic bacteria relative abundances including *Akkermansia muciniphila* and *Bifidobacterium* spp. [125].

Although the majority of studies have focused on bacteria in the gut microbiome, other reports demonstrated the importance of other microorganisms such as yeast. It was suggested that colonization with *Candida* spp. such as *C. albicans* could contribute to autism disorders by prohibiting absorption of carbohydrates and minerals and permit excessive build-up of toxins. *C. albicans* colonization was shown to enhance autistic behaviors in children having autistic disorders [126]. Similarly, another study proposed that it is the interaction between propionic acid and ammonia emitted by *C. albicans* that cause enhancement of autistic behaviors; this reaction produces an increased amount of beta alanine, which has been proposed to be an important contributor in autism spectrum disorders [127].

Likewise, GIT inflammation induces stress on the microbiome through the release of cytokines and neurotransmitters. Together with the increase in intestinal permeability, these molecules travel systemically. Increased blood levels of cytokines enhance the permeability of the blood–brain barrier, increasing the harmful effects of rogue molecules from the permeable gut; the release of these molecules influences the brain function, causing anxiety, depression, and memory loss [128–131].

## Natural treatment of adverse diseases caused by pathogenic invasion or microbiome dysbiosis

This survey illustrated that serious diseases and complications could take place in the case of altered microbiome community to pathogenic community or invasion of the host with foreign pathogens. In spite of conventional autobody defense, these aliments may happen leading to socioeconomic burden and poor quality of life. However, still there is a hope. God offers the humanity a kingdom of medicinal plants that hold thousands of natural compounds, which could be utilized as prodrugs for these critical maladies.

Herein, a few examples of biologically active compounds derived from plants are given:

Regarding cytotoxic and antiviral activities, genus *Solanum* involves a class of compounds named glycoalkaloids with promising antiviral and cytotoxic activities against various human carcinoma cell lines comprising breast, colon, liver, brain, leukemia, and melanoma carcinoma cells. In addition, glycoalkaloids possess antidiabetic and antimicrobial activities especially versus *C. albicans* [132–135].

Numerous medicinal plants such as *Balanites aegyptiaca* comprise antidiabetic principles. Saponins, isolated from these plants, could be ideal for antidiabetic treatment [136–138].

Fixed oil from *Balanites aegyptiaca* was reported to have antibacterial and antifungal efficacy in addition to cytotoxic and antiviral activities [139].

Plenty of flavonoid and coumarin phenolics compounds were reported for their pharmacological activities.

Bergapten extracted from different citrus species such as *Citrus bergamia* and *Citrus medica* cv. Diamante is reported to have antiproliferative efficacy versus melanoma cell lines [140].

Similarly, scopoletin and scoparone coumarins are reported to possess antioxidant and intestinal anti-inflammatory effectiveness [141].

Antibacterial potential of *Atropa belladonna* was associated with rutin flavonoids and xanthotoxin coumarin concentrations [142].

Flavonoids have the capability to exert human protective enzyme systems. A number of reported studies have suggested protective activities of flavonoids against numerous infectious diseases induced by bacteria and viruses in addition to degenerative diseases such as cardiovascular and cancers[143].

Methyl caffeate from *Solanum torvum* was reported as a promising antidiabetic [134].

Quercetin is documented to potentiate the effects of acyclovir against herpes simplex virus and pseudorabies infections. Quercetin was also reported to induce inhibitory effects on different malignant cell lines *in vitro* including leukemia, gastric cancer, colon cancer, human breast cancer, and human squamous and ovarian cancer cells [143].

Likewise, kaempferol flavonoid is present in many traditionally used medicinal plants such as *Ginkgo biloba*, *Tilia* spp., *Equisetum* spp., *Moringa oleifera*, and *Sophora japonica*. Many preclinical investigations have illustrated that kaempferol and some kaempferol glycosides have a vast range of biological performance, such as antioxidant, anti-inflammatory, and antimicrobial leverage. Other important activities comprise anticancer, cardioprotective, neuroprotective, and antidiabetic effectiveness. Similarly, antiosteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic effectiveness were also reported [144].

## Conclusion

The behavior of the human microbiome could be extremely changeable from symbiotic microorganisms to pestilent ones. Many internal and external factors influence this newly conducted attitude. Impaired immunity, unregulated microbiome, and antibiotics are considered as the characteristic involving factors.

### Future prospective

Both commensals and conventional pathogens change their response to the body host based on the surrounding environment, shifting either more harmful or less harmful ones. The net result is that upon disease incident, we have to deal with the resultant pathogens.

As future prospective, we have to work hard to cross the barrier of applied sciences to bring the natural possible prodrugs to real available medicament.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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