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REVIEW ARTICLE OPEN ACCESS

Gut Microbiota: A Future Clinical Magic Bullet to Manifest Pathogenic Disease in the Current Future

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Abstract

Microbes proved to be the significant biotic factors that influence the health of humans. Gut microbiota remains an emerging field for understanding different aspects of microbiology, immunology, computational biology and food and nutrient supplementation studies. The human microbiome project provides a thread in the path of microbe association with humans. This review will discuss how their study was taken last year on human microbiome discovery for human health. Thus, the microbiome could be deliberated as target for treating various disorders. Despite some limitations, interventions in this field of study appear encouraging for emerging a preventive therapy by restoring microbiome functionality or as an adjuvant in specific immunotherapy. Manipulation of the gut microbiota in various disorders is assessed by examining the current most relevant evidence concerning to antibiotics, probiotics, prebiotics, polyphenols, and fecal microbiota transplantation. This review discusses the impact of gut microbiota on health and their manifestation by focusing on vital mechanisms.

Keywords: Microbiota, Disease, Nutrient, Intestine, Dysbiosis

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INTRODUCTION

A microbiome is defined as the set of microorganisms living on or inside living organisms. This microbiome includes bacteria, fungi, viruses, and protozoa that consist of 150 time's greater genetic material than that of the host.[1] The well-studied niche microflora is inside the human gut, where about tens of trillions of microbes live symbiotically. Phyla*, Firmicutes, Bacteroidetes, Proteobacteria,* and *Actinobacteria* are, more prominent in healthy adults.[2] When the species of different class of microbes are deregulated, it contributes to several complication related to the health. In human body, colon contains the highest microbial diversity that is present on earth. In human gut *Bifidobacterium, Bacteroides, Prevotella, Fusobacterium, Eubacterium, Peptococcus, Peptostreptococcus Ruminococcus,* class of *microbes abundant. Escherichia* and *Lactobacillus.* Bacteroides alone constitute about 30% of all microbes in GI tract.[3] Innate and adaptive immune systems of host also contributed by microbiome.[4,5] Dysboisis of microbiome cause inflammation and autoimmune diseases.[6-8] Intestinal dysbiosis deregulates metabolic activities which are highly associated with host factors like age, diet, and environmental conditions.[9] Accompanying mechanistic exploration toward host microbe interaction, in 2007 human microbiome project (hmpdacc.org) started focused on identifying and characterizing human microbial flora.[10] Hence intestinal microbe can be major target for health improvement.[11]

Microbiome specific disease diagnosis, monitoring and treatment may revolutionize much incurable drug dependent disease worth anticipating. Microbiome technologies are expected to play a crucial role in the development of new drug discovery platforms and companion diagnostics in the precision medicine era (Figure 1).

Common Enterotype in Gut Ecology

Human gut microbiome has been classified into three distinct enterotypes (*Bacteroides, Prevotella*, and *Ruminococcus*). Gut microbial enterotypes are associated with specific fooding habits and drug intake patterns. *Prevotella*- are enriched in people consume carbohydrate diet. While high protein and fat diet intake dominate *Bacteroides*- population. *Ruminococcus*-dominant enterotype is associated with grain Lovers. 16S rRNA gene of human intestinal tract microflora explores diversity measurement.[12,13] Metagenomics studies also characterized functional microbiome among American and Japanese individuals. The intestinal flora includes *Lactobacillus, Bifidiobacteria, Peptostreptococci Propionibacteria* and *Enterococci.*[14,15] Primary function of these microorganisms is to live in commensal and protect gut after secreting antibiotic substance that inhibit the growth of harmful microorganism and maintain pH that is essential for intestinal wall to perform protective barrier, and provide an environment where microbe cannot colonize.[16-20] Opportunistic flora, of intestinal include *Clostridia, Bacteroides, Staphylococci, Streptococci, Bacilli, Yeasts, Peptococci Enterobacteria, Fusobacteria, Eubacteria, Catenobacteria* and others. The flora which enters the body through food and drink constitutes the transitional flora.[21] Dysbioisis of microbiome cause inflammation and autoimmune diseases,[6-8] promoted by loss of intestinal barrier function, against which an immune cascade get activated (Figure 2)

Psoriasis and Psoriatic Arthritis

Psoriasis is an autoimmune disease in which skin cells grow faster than normal and formed a bumpy red patch covered with white scales.[22] Several studies on surface or skin microbiota confirmed the elevated *Staphylococcus* and *Streptococcus* genus.[23] In psoriatic patient bacterial DNA has been isolated both locally and systemically, and altogether evidence a central role of bacteria in psoriatic disease.[24]

Prolonged psoriasis illness cause damage of tissues and bone which resulted in psoriatic arthritis.[22] Gut microbiota study of psoriatic patient clear the abundance of *Prevotella copri*.[23] Decrease Bacteroides genus and an increase in the numbers of *Faecalibacterium, Akkermansia,* and *Ruminocuccus* genera is also a characteristic findings in the gut microbiome of patients with psoriasis.[11] African cluster study found that *prevotella* species, predominantly contributes to the joint inflammation in the intestine. Auto reactive T cells turn out to be highly reactive

to auto antigens, including arthritis specific antigens, via activation of innate immunity.[24,25] These T cells populations can then exacerbate joint inflammation. Presence of bacterial DNA in psoriatic patient plasma confirmed.[26] This increased bacterial load in blood arose from intestinal barrier disruption, along with their metabolite access to blood stream and skin homeostasis impairment.[27,28] These findings established a correlation between the gut microbiome and skin homeostasis. Psoriatic skin had less *Propionibacterium* and *Corynebacterium* had less *Ruminococcaceae* and *Akkermansia* but more *Bacteroides* and *Faecalibacterium*.[28,29] Intake of oral probiotic of *Bifidobacterium* infantis35624 reduced the plasma levels of TNF-α as compare to control.[30] Oral administration of *L. salivarius* LA307 and *L. rhamnosus* LA305 showed reduction of eczema and inflammation marker.[31] In imiquimod-induced psoriasis mouse model *L. pentosus* GMNL-77 and *Lactobacillus* sporogenes administration (as a probiotic) were able to suppress TNF-α, IL-6, and proinflammatory cytokines in the IL-23/IL-17 cytokine.[32]

Inflammatory Bowel Disease (IBD) and Colitis

Chronic Inflammation of small intestine, colon and Crohn's disease (CD) and ulcerative colitis (UC) are called inflammatory bowel disease.[33] Gut dysbiosis, and dysfunctional immune responses cause intestinal tissue damage by activated Th1 and Th17.[34] Mucosal injury results in invasion of microbial antigens, TLR ligands that perpetuate the immune responses.[35] NOD2 gene present in human encodes intracellular pattern recognition receptor that recognizes bacterial peptidoglycan and stimulates immune system.[36] A report showed that NOD2 gene knockout in mice tends to decrease IL-10 and increased susceptibility to colitis, in human subjects with NOD2 mutations.[37] Increases in the *Gammaproteobacteria* and decreased abundances of bacterial taxa of

Figure 1. Human gut microbe has a close relationship with diseases of different system

Firmicutes and *Bacteroides*.[38,39] Most common microbes present in inflammatory bowel disease patient is Rhodotorula, which is capable of inducing intestinal inflammation.[40] transfer of these bacteria induces inflammation in healthy mice. In CD bacteria which produce short chain fatty acid *Phascolarctobacterium* and *Roseburia* are also reduced while *Leuconostocaceae* is depleted in UC along with enrichment of *Escherichia* species and a depletion of *Faecalibacterium* species.[41,42] *Bacteroides vulgatus* bacteria alter mucosal membrane function and turn on inflammatory genes.[43,44] Nonpathogenic strain of *E. coli* used as prebiotic has been shown effective in patients of ulcerative colitis.[45] *B fragilis* prevents colitis in mice by interacting with CD4 Foxp3 regulatory T cells which produce IL-10.[46]

Therefore bacteria and fungi can penetrate mucosal barrier and activate TLRs, CARD9 and Decting-1 activation resulted in more severe phenotype in lamina propria.[47,48] When CARD9 knockout in mice, they got susceptible to colitis. This susceptibility was directly associated with tryptophan metabolism correlated to impaired microbial population.[49]

Carbohydrate fermentation products, propionic acid, acetic acid and butyric acids which play important role in activation and regulation of multiple pathways specific to colon.[50] Among all metabolites butyrate significantly involved in colonocytes metabolism.[51] This imparts anti-inflammatory action by inhibiting IL-12 and TNF-α cytokines and up regulating IL-10 in human monocyte.[52] Expansion of T-Cell to mitigate intestine inflammation induces by Bacteroides and *Clostridium* species.[53] Previous studies on IBD suggest that combination probiotic of *Bifidobacterium breve, Bifidobacterium infantis, B. longum, L. acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Streptococcus thermophiles,* and *Lactobacillus bulgaricus* have potential to reverse ulcerative colitis.[54] Mesalamine, an anti-inflammatory drug decreases the Escherichia/Shigella in IBD and attenuates intestinal inflammation.[55,56]

Liver Diseases

Liver is the major vital organ that detoxifies the body and support function of other organs. Failure of liver function can leads to serious health complication. Relation between liver diseases and gut microbiota has been well established.[57]

Imbalance in pathobiont and beneficial bacteria is associated with deleterious effects on host and plays a critical role in the development

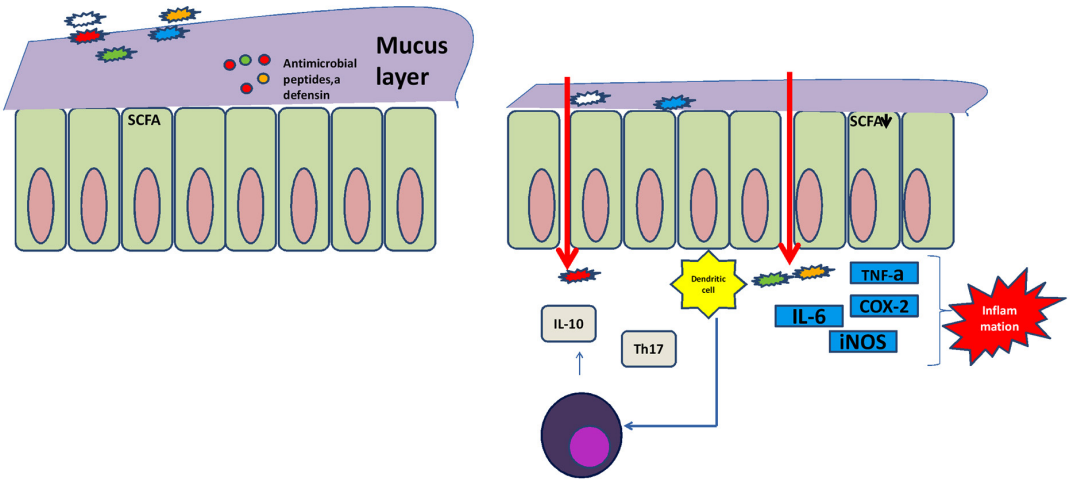

Figure 2. Presentation of eubiosis and dysbiosis difference in intestine, microbes maintain gut membrane stability with production of certain metabolite (i.e short chain fatty acid, butyrate) and prevent microbial expansion. In dysbiosis specific microbe's overgrow and metabolites changes in absence of specific species increase production of proinflammatory cytokines such as IL-6, IL-17, TNF-α and cause inflammation

of alcoholic liver disease,[58] nonalcoholic fatty liver disease,[59] nonalcoholic steatohepatitis,[60] acute (toxic) liver injury, fibrosis/cirrhosis, hepatic tumors,[61] autoimmune hepatitis and autoimmune cholangiopathies.[62] These disorders arise from translocation of bacterial metabolites by intestine to liver.[63] These endotoxin metabolites received via toll-like receptors and cause damage to liver associated with higher levels of serum TNF-α, IL-6, and adipokines 2.[64] Moreover, bile acid dysregulation linked to dysbiosis, hepatic lipid accumulation increases insulin resistance, and inflammatory signaling.[65]

When infection of *Streptococcus pneumonia* increase in liver, a protein that is reactive to the C-polysaccharide of bacteria called as C-reactive protein take part in antigen removal.[66,67] Concentration of CRP in blood directly proportional to inflammation in response to infection, trauma, and tissue infection, Hence, the CRP is monitor in various inflammatory conditions.[68] Higher faecal proportions of *Bifidobacteria, enterobacteria* and streptococci associated with alcoholic hepatitis.[69]

Thus, intestinal microbiota is center for progression of alcoholic liver disease. Conversely, *Proteobacteria, Bacteroidetes,* and *Enterobacteriaceae* were found to be increased in NASH patient as compare to healthy controls, while *Firmicutes* declined.[70] Hence Bacterial translocation cause systemic infections in liver of Proteus and *Enterobacter* which have ability to bypass the intestinal barrier and associated with higher incidence of bacteremia. In liver cirrhosis, population of *Bacteroidetes* is significantly reduced, while *Proteobacteria* and *Fusobacteria* increased.[71] Mixture of *Bifidobacteria, Lactobacilli,* and *Streptococcus thermophiles* probiotic was able to reduced high-fat diet (HFD)-induced steatosis, inflammation, and insulin resistance in a rodent model.[72]

Obesity and Type 2 Diabetes Mellitus

Obesity and diabetes are the third most common disease in aged people after cardiovascular disease and cancer.[73,74] It's a debate where obesity cause type 2 diabetes, high blood pressure and heart disease or because these illness person became obese.[75] Obese people are always on risk of developing type 2 diabetes. In obese persons, fat tissues cells have to process more nutrients than their regular capacity.[76]

In metabolite study of plasma and stool samples 19 metabolites associated with BCAA (branched-chain and aromatic amino acids) linked to high BMI and obesity development.[77] Diet consisting saturated fat, associated with increased inflammation with abundant white adipose tissue (WAT) and metabolic disease, on the other hand polyunsaturated rich diet counteract inflammation and promote healthy lean phenotype due to changed metabolism.[78] Fat induced WAT accumulation occurred as a result of inflammation, mediated through gut microbial activation of TLR4 which serve as receptor for microbe-associated molecular pattern (MAMP) receptors, and further activate proinflammatory response through nuclear factor (NF)-kB pathway, producing antibacterial products, cytokines and chemokines.[79] Studies performed in different diabetic group shown lower intestinal Roseburia and Bacteroidetes. Abundant *Faecalibacterium prausnitzii* (both butyrate producing bacteria), and other strains *Lactobacillus gasseri, Streptococcus mutans*, *Firmicutes* and *Clostridiales* members also contributes to disease.[80]

In a experiment where germ free mice inoculated with obese (ob/ob) or lean (+/+) microflora. Mice that received obese microbes extracted more calories from their food and increase in total body fat than in mice colonized with lean microbiota. In one study author insert the lean phenotype microbiota in obese phenotype, and find improve insulin sensitivity.[81] Resistance of insulin reported as a increase in branched chain amino acid which are associated with gut microflora.[82] Changes in metabolites related to obesity were directly linked to four different bacteria (*Ruminococcus, Blautia, Dorea* and in the *Lachnospiraceae* family, and SHA98.[83] Supplementation of *A. muciniphila* reduced inflammation reduces LPS level and improved glucose tolerance.[84,85] Fermented probiotic fiber has potential to protect against metabolic syndrome[86] consequence of reduced intestinal permeability.

Atherosclerosis

Atherosclerosis is the deposition of fat molecule on artery wall, Plaque of fat and other

minerals reduce the diameter of artery for the flow of oxygenated blood. There are some factor like high LDL, obesity, smoking and consumption of unhealthy diet results of this condition along with family history. Western diet comprises diet reach in choline and carnitine have increased risk of cardiovascular disease.[87,88] Gut microflora convert these compound into trimethylamine (TMA), which is further interconvert into trimethylamine-N-oxide in the liver and trigger heart problems.[89-91] This conversion of TMA catalyzed by microbial TMA lyase. Atherosclerosis development triggered by TMA through up regulation of the CD36 of macrophages and promotes uptake of cholesterol and formation of foam cells.[92,93] Reduced expression of cytochrome P450 7A1 and 27A1 which metabolize drug and other molecule in liver, and promotes vascular inflammation by activating nucleic acid factor-κB signaling pathway, monocytes through mitogen-activated kinase.[94-96] Inhibits cholesterol reverse transcription.[97,98]

Gut microbiome composition in atherosclerotic patients observed to be more inflammatory.[99] Elevated *Escherichia coli, Klebsiella* spp., *Enterobacter aerogenes, Streptococcus* spp., *Lactobacillus salivarius, Solobacterium moorei,* and *Atopobium parvulum*. Depleted abundance of gut species such of *Bacteroides* spp., *Prevotella copri*, and *Alistipes shahi*[100,101] has been recorded in patient. Administrative study of *Lactobacillus plantarum* as probiotic reduce blood cholesterol and therefore restrain the formulation of atherosclerotic plaques in hyper-cholesterol patients.[102] When *A. muciniphila* supplemented in atherosclerosis prone mice, it protected atherosclerosis development while mice were feed on Western diet.[103] Indeed, mice harboring high choline-metabolizing bacteria are susceptible to diet-induced metabolic disease.[104] Secondary metabolite of polyphenol class like Gallic Acid α-Asarone, Equol, Urolithins and Quercetin-3-glucuronide function in protection of cardiovascular system.[105,106]

Microbial metabolism modulation through diet intervention or direct supplementation provides effective strategy for prevention of cardiovascular diseases.

Ageing

Aging is a consistent decline in vital activities that is associated with inflammation. Age dependent changes are associated with oxidative/genotoxic stress and change in gut microbiota composition by the time.[107,108] *Bifidobacteria* by the span of life decline, whereas *Clostridium perfringens*, *Lactobacilli,* and *Enterococci* increase with age.[109] Composition change of gut microbiota directly correlated with intestinal inflammatory state.[110] Current studies on microbiome and aging associated changes evidenced the role of certain population which regulates pro-inflammatory and anti-inflammatory networks in the gut microbiota.[111,112] Inflammatory markers such as LPS-binding proteins increase in aged healthy person.[113,114] Hence low grade inflammatory status facilitates by LPS.[115]

Malaria

Malaria is a mosquito transmitted disease affect 219 million population yearly, *Plasmodium* species is causative agent. Different mice studies showed that mice devoid of commensals bacteria are more susceptible to *Shigella flexneri, Bacillus anthracis,* and *Leishmania infection.*[116,117] Moreover, gut microbiota can diminish intestinal immunity and increase susceptibility toward enteric pathogens such as *Citrobacter rodentium* and *Campylobacter jejuni.*[118,119] Providing the importance of the microbiota in regulating immune system function homeostasis.

Mice study Demonstrated *E. coli* expressing a-galactosyl, host were protected from effective Plasmodium liver-stage infection.[120] Influence of the microbiota on the progression of malaria clinical outcome infections has only now started to emerge.

Absorption of Vitamin B12

Vitamin B-12 or cyanocobalamin is essential co-factor for iron metabolism as well as nucleotide synthesis and neuronal system function. Deficiency could introduce tiredness, anemia, constipation, weight loss, memory problems, and neurological issues.[121] Major problem arise either deficiency in food or malabsorption due to lack of bacterial population helps in interconversion in intestine.[122] Cobalamin deficiency cause less cell division, neuropathy, nervous system disease, and pernicious anemia.[123] B12 deficiency is prevalent in vegetarian diet people as plants are not a source.

Concentrations of cobalamin can be detected in fermented food.[124] An intrinsic glycoprotein factor secreted by gastric mucosa serves as important absorption factor. Cobalamin deficient patient's microbiota showed dramatical changes after cyanocobalamin and methylcobalamin supplementation.[125] Methylcobalamin alleviate butyrate producing bacteria which may alleviate intestinal inflammation. Previous studies confirmed that vitamin B12 deficiency is also contributes to inflammatory bowel disease.[126]

Neurological Disorders

Gut is also called second brain of human, so disorder in neurological system state the gut health disturbance that is consequence of microbe ecosystem misbalance.[127] Neurological complication aroused due to failure of gut membrane function that allow other microbes and their metabolites to blood stream as a loss of permeability,[128] Which may disrupt the synthesis of SCFA (short chain fatty acid) served as vitamin and hormone cofactors,[129-131] and generate molecules that reduce inflammation,[132] and play a function to boost immune activities. Medium chain fatty acid, alpha lipoic acid which is the activator of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) which response in antioxidant element signaling pathway.[133,134] Increased inflammation of gut linked to neurodegenerative diseases.[135-137] Gut microbiota alteration have been directly linked with mental comorbidities like depression, multiple sclerosis and Parkinson disease. Structural, biochemical or electrical abnormalities in the brain, spinal cord cause physical impairment such as neuromyelitis optica spectrum disorders, multiple sclerosis, Parkinson disease, Alzheimer disease, Huntington disease, and amyotrophic lateral sclerosis.[138-142] Enrichment of Archaea (genus Methanobrevibacter) was relative to controls as well as depletion of members from the *Firmicutes* (eg, *Clostridium genera*) and *Bacteroidetes phyla* reported. Consumption of antioxidant throughout life can also impede neurological symptoms along with enhancement of immune system. Neurological diseases are mainly can be cured through cleaning of colon. Certain Ayurveda remedies also showed very tremendous result after a panchkarma procedure of "Basti" (rejuvenation of large intestine).[143]

Depression and Anxiety

Role of gut microbiome has been implicated in various disorders, with particularly strong evidence for its role in depression and neuropsychiatric disorder.[144] Post gut microbiota transfer of depression patient healthy mice showed elevated level of tumor necrosis factor alpha (TNF-α).

Interleukin-6 (IL-6), interleukin-8 (IL-8), along with C-reactive protein (CRP) and higher kynurenine/tryptophan ratio. Total blood cortisol was also increased which is reflecting stress environment in body. Patient data showed

Profound difference in *Prevotellaceae* family and *Prevotella* genus. Short chain fatty acid, plasma lipopolysaccharide binding protein did not directly correlate. Although, *Alistipes, Faecalibacterium,* and *Ruminococcus* were correlated with a detectable level of isovaleric acid.[145] Response of gut microbes is gender biased; *Lactobacillus rhamnosus* did not improve stress in male.[146] Protiobic species *Lactobacillus helveticus* and *B. longum* are able to reduce depression in patients with major depressive disorder (MDD).[147] These results are contradictory with negligible effect on clinically depressed patients.[148] Although, animal model able to produce the human relevant data, but investigation of human samples to establish a proper relationship investigating mechanism behind it is needed. Encouraging results of probiotics.

Cancer

Cancer is a leading cause of death worldwide. In 2018, cancer accounted for 9.6 million deaths.[149] Role of numerous gut populating bacteria, have been recognized as protectant against the tumors genesis.[150] *Lactobacillus rhamnosus* GG (LGG).

Is the most studied probiotic for cancer intervention studies.[151] In colon cancer patient, change in bacterial community has been reported with abundance of pathogenic bacteria.[152] *Lactobacillus* and *Bifidobacteria* prevent tumor development by MyD88 suppression, which play essential role in developing carcinomas.[153,154] *Lactobacillus johnsonii* modulate immune system in colorectal patient by *Enterobacters* modulation.[155] In an experiment with colonized *Helicobacter hepaticus* mice exhibit colonic Th17

inflammatory molecule also have a beneficial role in human ovarian cancer.[156,157] murine melanoma, pancreatic and colon cancer.[158,159] *Helicobacter pylori* is known for alter stomach pH and acid reflux, which could protect against Barrett's esophagus and esophageal cancer.[160,161]

Kidney Disease

Various combination of different type of disorders like high blood pressure, diabetes, urinary tract obstruction, kidney stone, enlarged prostate are also part of pyelonephritis. In kidney disease lower intestinal microflora has been found to be altered mostly associated with decreased *Prevotellaceae* and *Lactobacillaceae* families.[162] Analysis of fecal microbiota showed overgrowth of aerobic bacteria, such as *Enterococci* and *Enterobacteria* species, was 100 times greater in hemodialysis patients along with Lower numbers of *Bifidobacteria* and higher *Clostridium perfringens*.[163] In Chronic Kidney Disease urea secrete into the gastrointestinal tract where hydrolysis of urea takes place by urease which is expressed by some gut microbes. Ammonia produced in gut which can affect the growth of commensal bacteria.[164] Mild consumption of fiber diet, use of antibiotic, intestinal wall edema, and oral iron intake, metabolic acidosis also cause dysbiosis.[165] Nephroprotective metabolite such as vitamin K and butyrate lowered due to microbes producing (e.g., short chain fatty acids), such as *Lactobacillus*.[166] Gut bacteria *Clostridium* and *Bacteroides generate* some toxin and metabolite (phenol, indole) which later absorbed in blood and filter by kidney. Plasma metabolites of hemodialysis patients confirms the

Colonic origin of indoxyl sulfate and p-cresol which is fermented product of phenylalanine and tyrosine.[167]

Factor that influence gut microbiota

Several intrinsic and extrinsic factors can influence gut microflora composition, some extrinsic factors like Diet/lifestyle, Drugs/Antibiotic, Age, Host immunity, and intrinsic factor involved genetic factors.[168] There is some most studied factor that has been proven to alter gut microbiota.

Diet

In our routine life diet that we consume daily affect the microbe health in our gut. Reports showed that changing of fooding habits alter the microbe makeup in gut. Previously a mice study showed decline in gut microbial diversity after having high fat diet (60%). In diabetic patient *A. muciniphila* decreases, treatment with *A. muciniphila* reduces fat content. Among different kind of diets fiber rich diet is proven to be beneficial and associated with gut microbiota modulation.[168] Composition of gut microbe varies to the consumed diet; *Bacteroides* composition is associated with protein and high animal fat diet. On the other hand *Prevotella* is more common to carbohydrate diet. Hence diet is associated with enterotype partitioning. The high-fat diet contributes to dysbiosis which ultimately caused disease.[169] Strong health benefits evidence of fermented foods and beverages are reported in several diseases with their significance on the gut microbiota balance.[170] Incorporation of fermented foods diet (e.g., kimchi, kefir, etc.) may counter the proinflammatory effects of gut dysbiosis.[171]

Infections

Some pathogenic microbe's secreted metabolites can inhibit gut microbes growth. In a study where researcher showed *Citrobacter rodentium* enteropathogenic effect on the mice microbiota, reduced abundance of *lactobacillus*. *Clostridium Difficile* presence cause severe dysbiosis in gut microflora. In human infected patients microbiota studies in mice data showed transplantation results in high microbial richness and diversity. It is clearly proven by previous results that shift in the host microbiota have potential to clear infections and pathogenesis as well.

Medications

When people have any symptom and disease complication various medicines recommended in response to cure illness but some of them cure the disease but affecting the gut bacterial diversity. Antibiotics are the most commonly used class of drug prescribed for any type of infection and illness but showed a profound effect also, which could be persistent. Antibiotic consumption in neonate cause symbiosis, which may be an inclining factor to inflammatory bowel disease and obesity.[172]

Genetics

Host, microbiota and environment contribute or affect the genetic makeup of species. Presence of gut bacteria is influenced by genetic makeup affecting host metabolism and causing disease.[173] As like common genetic makeup sibling or parent also showed similar microbiota communities than unrelated individuals. In monozygotic twins gut microbiota is reported to be similar to dizygotic twins as genotyping and metagenome analysis showed.[174]

DISCUSSION

Diversity of microbes in gut allows degrading the complex constituents of diet and executing numerous vital activities that are essential for metabolic and immune functions. Intestine outer layer secrete mucin for protection from proinflammatory compounds and uptake of antigens, gut microbiota has long been believed to maintain, intestinal structure and cells function for providing better health.[175] Butyrate is the metabolite produced by obligate anaerobic bacteria which stimulates mucin secretion from intestinal surface along with antimicrobial peptide; this secretion is as unique as your fingerprint. In 2007 NIH supported human microbiome project launched aiming, gut microbiome research experimental methodologies, new computational/ statistical approaches for microbiome data analysis or a microbiome-based product or device. Past and present research implications confirm the role of microbiota to all aspect of development and host's growth. Different practical efforts showed that imbalance in composition, habitat, or numbers of the gut microbiota tend to dysfunction in human is absolutely correlated. Many unsolved mysteries about microbe still remain unclear in the interactions study of host and the microbiota and their impact on the disease process. It is new field full of new promises, idea and unsolved biological questions that can expand knowledge in understanding of human pathophysiology. High-throughput sequencing data provides more information which support microbiology techniques and bioinformatics platforms in elucidating mechanisms of microbial community impact on human health. Study on human microbes can only be possible with current available machine based techniques and computer programmer. Microbes identity

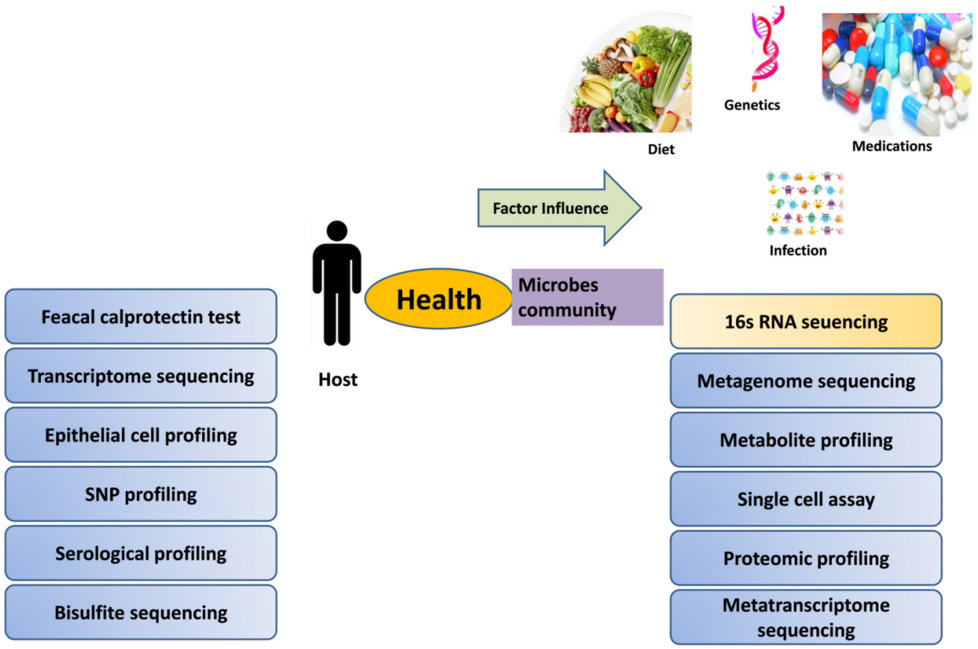

Figure 3. Tools and techniques employed in host parameter and microbial diversity detection during disease pathogenesis along with influenced factors of gut microbial diversity

can be distinguishing with the help of bacterial ribosomal RNA (rRNA) genes sequencing, 16s ribosomal RNA is highly conserved gene among prokaryotes.[176] Modern laboratory tools employed 16s rRNA and metagenomic sequencing enabled us to gain quantitative identification of microbes present in a sample (Figure 3). Phylogenetic information of microbiome attained using shotgun DNA sequencing approach, along with additional understanding of complex functions of these communities by identifying their genes. Customization of microbial consortia using advanced culturomics allows microbes interaction studies under complex system. Artificial intelligence in leading so many predictability in study field like microbe composition could predict age. Microbiome sequencing data obtained from fecal (gut microbiota), saliva (oral microbiota) and skin samples from several continents has been processed with bioinformatics pipeline by IBM researcher to ensure coherence and compatibility of the data.[177] Hence gut microbes proved to be a health modulator, more researchers from different scientific background focus on how this advanced technology will continue decoding the gut microbiota potential in personalized medicine development.

Characterization of oral cavity, skin microbiota may help us to better understand the complex gut microbiome-host interactions. International Human Microbiome Consortium (IHMC) provides a platform to access, data linking, and microbial sequences with human phenotype. These data bases and bioinformatics tools enables researcher to segregate diverse population and target potential groups for interventions. Human genome shape the structure of gut microbial composition. Expression of lactase gene responsible for lactose digestion has high *Bifidobacteria,* and *Ruminococcus* torques which correlates to fucosyl transferase (FUT2) gene.[178] By microbe and genome interaction important metabolic pathways regulated in host that are important aspects of nutrition and immunity. So human disease and bacterial species analysis stretch can establish interrelation within microbes and host. *Bifidobacterium* abundance lowered the risk for inflammatory bowel disease ulcerative colitis, this observation also reported in previous clinical trials. Food majorly impact structure design of gut microbiome. Type of food and dietary patterns directly influences the prevalence of different types of bacteria in the gut, which affect human health through modulating metabolic pathways. It could be said that you feed your microbiota and are fed by them. Consumption of plant-based foods diet is more prone for developing "good" gut microbes. While processed plant food are associated with bad gut microbes. Mice feeds on the preservative component which are common to packed food (food emulsifier, processed sugar carboxymethylcellulose, polysorbate-80) showed enhanced expression of proinflammatory cytokine genes along with decrease *Bacteroidales* and *Verrucomicrobia* which promote mucus associated inflammation.[179,180] Laxative drugs like progesterone, rupatadine and TNF-α inhibitors changed 10% of community variation in Dutch-Belgian population. Prebiotics are microbes growth promoting food such as fiber-rich foods, fruits, vegetables, and whole grains, while probiotic is bacterium or fungi that are taken as a supplement for proper body function, that occur in many fermented foods, including yogurt, sauerkraut, and tempeh. Consumption of fermented food gets you the live microbes that are present in them and improve intestinal permeability, balancing and barrier function. Dysbiosis is the cause of many disorders and reestablishment of symbiosis by introducing microbes could hold the key to new effective therapies. Probiotic or prebiotic interventions serve to increase beneficial microorganism's growth and metabolism in the host. Restoration of the gut microbiota with the use of probiotics has led to promising results in clinical studies.. Microbiomics has incited interest pre/probiotics for management and control human health. Probiotics are reported to lower the inflammations which are reported to be elevated IgE, IgA, IL-10 and CRP. Probiotics, prebiotics, and their combinations clinically proved effective against gut disorders like IBD, digestion, traveller's diarrhea.

Emerging areas of research provide promising cancer, brain, kidney, and obesity management since tools for probiotic research are now available. Therefore probiotics, prebiotics open up a new branch of science, flagging a new way toward personalized medicine, and future biotherapeutics. Phytochemicals consumption

improve gut barrier integrity by activating tight junction expression and serving as antioxidant to induce stress resistance mechanisms in the gut by maintaining homeostasis, including autophagy, DNA repair, and expression of detoxifying and antioxidant enzymes., that helps to prevent chronic diseases, and prolongs lifespan. Phytochemicals that provide immunomodulatory potential first strengthen the gut system as gut is site of high immunological active cells. Much more emphasis should be given to phytochemical-microbiota reciprocal interactions, biotransformation of phytochemicals and plant-derived drugs, and pre-clinical and clinical efficacies of herbal medicine on dysbiosis. This will provide newer insights for future pre-clinical and clinical phytopharmacological interventions.

Based on experimental evidences companies are focusing on production of product help to establish healthy gut ecosystem. Probiotics supplemented food products cover $7.10 billion market by 2026 and increase of market based therapeutic in 2019 compared to 2018. Therapeutic marked goes down in 2020 due to covid-19 outbreak. Along with natural state microbes, other therapies also working on genetically-modified microbe. Microbiota being transferred via enema, colonoscopy, pills and nasogastric routes in patients. Keeping the benefits in mind National Microbiome Initiative set up goal to support microbial research and expanding it to pharma companies. Johnson & Johnson, Nestle, Seres Therapeutics, named little precision / personalized medicine which includes the microbiome, more companies are also working toward this approach.

Wellbeing role of microbiota open a window of nutritional and pharmacological opportunities to improve host-microbe relationship. How we respond toward certain drugs by enzymatic conversion it also depend on microbial type. In current world bacteriophage therapy is the only used in certain cases for patients in therapeutic failure, and are always accompanied by antibiotic treatment. Emerging phage therapy approach, which comprises phages and their derived protein against multi drug resistant bacteria. Phage lysins are more feasible therapeutic tool as they are not immunologically active and purification and production are accessible with safe storage. Extensive progress in last years has given deep insight to immunology and disease pathology with increased therapeutic pathways/targets exploration opportunity.

CONCLUSION

Gut microbes form the largest complex ecosystem in the human body which benefits the host by producing cometabolites. These metabolites depend on the type of food consumed by the host and also determine the microbiota composition, which later participates in vital activities connecting organs and mental health. Scientific interests focused on exploring more about microbes relation to host and their diseases got increased in the last years. Manifestation of fecal microbiota transfer, phage therapy, prebiotics, and probiotics approaches are getting success in controlling disease. Along with diet, other internal and external factors also disturb gut microflora composition that causes non-communicable diseases or increase susceptibility to communicable diseases. A short-chain fatty acid-containing diet regulates immune cell migration, mucosal permeability, and anti-inflammatory response and maintains a redox environment. More research carried out on the relationship between diet and host health provided evidence of an important role in human physiology and health in terms of pathogen invasion prevention and immune system maturation. Microbiota studies provide a base to design personalized medicine targeting gut microbiota for the ailment of a range of disorders in near future. Researchers have developed GI bacteria culturing techniques and metagenomic sequencing to overcome the limitation in this area. Microbiome ecology inspired use of live therapeutics to treat patients through additive, subtractive, and modulatory therapies. Pharma companies should focus on manufacturing bacteria-specific products having proper strain genomic characterization and minimal side effects. Functional network of these discipline come on front and provide a remarkable opportunities for diverse research avenues, emphasizing human medicine and biotechnology.

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