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Review Article

Impact of Dietary Modification on Microbiome: Exploring Therapeutic Implications

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Abstract

The Human Gut Microbiome: The gastro-intestinal tract and various other organs harbour large and diverse communities of bacteria, viruses, and other microscopic life. In the human gut, there inhabit microbial members as residents (autochthonous), while others (allochthonous) are from ingested food, water and other components of the environment. The adult human gut microbiota is dominated by mainly two bacteria, the Bacteroidetes and Firmicutes and an archaea, Metanobrevibacter smithii.

The Gut Biosphere and Ecosystem: In general, the gut microbial community depends on their specific enzymes to utilize available nutrients, cell-surface molecular appendages to attach to their right habitat, evade bacteriophages, ability to deal with immune system and avoid washout and genetic mutability to stay well-adapted. The microbial ecosystems through the molecular processes influence various aspects of human metabolism and physiology. On the other hand, the host factors, such as dietary factors influence the host-microbial and microbial-microbial relationships.

Microbiota, Health and Disease States: Based on various clinical and animal studies, there has been documented a link between the gut microbiota and mental health. There exists a bidirectional microbiota-gut-brain communication which modulates brain function and behaviours. The microbial antigens or metabolites produced by members of the gut microbiome appear to improve the immune sensitivity to tumour cells, whereas the dysbiosis may cause loss of antitumor immunity. On the one hand, the inherent gut microbial enzymes and other molecules influence drug activation, efficacy and metabolism. The imbalances in the composition of the bacterial microbiota, known as dysbiosis, appears to be a major factor in various gastrointestinal disease states and extra-intestinal disorders.

Impact of Dietary Constituents on Microbiome: It is documented that a change in diet can alter the degradative activity of the colonic microbiota in vivo and in a physiologically relevant setting via influencing the expression of various microbial genes. Whereas, a diet low in dietary polysaccharides and fibre can trigger dysbiosis, degradation of the intestinal mucin layer and affecting intestinal health. The gut microbial production of short chain fatty acids and other metabolites has been documented to influence immune system.

Conclusion: The review article aims to highlight that dietary components influence and alter the composition of the gut microbiome. There are various studies that have documented the dynamic effect of altering host diet on the microbiota in the gut and other organs, with potential implications for disease modification and treatment.

Keywords: *Gut Microbiome; Microbial Dysbiosis; Drug Metabolism; Oligosaccharides; Polysaccharides; Probiotics; Prebiotics*

Introduction

The gastro-intestinal tract and various other organs including skin, respiratory tract and lungs, and genitals harbour large and diverse communities of bacteria, viruses, and other microscopic life. In the human gut, a nutrient-rich environment, reside ~ 100 trillion (10^{14}) microbes, the vast majority of which is present in the colon. There inhabit microbial members as residents (autochthonous), while others (allochthonous) are from ingested food, water and other components of the environment. The adult human gut microbiota is dominated by mainly two bacteria, the *Bacteroidetes* and *Firmicutes*, and archaea, *Metanobrevibacter smithii*.

In general, the gut microbial community depends on their specific enzymes to utilize available nutrients, cell-surface molecular appendages to attach to their right habitat, evade bacteriophages, ability to deal with immune system and avoid washout and genetic mutability to stay well-adapted. The microbial ecosystems through the molecular processes influence various aspects of human metabolism and physiology. Further, the human intestinal epithelium senses the presence of various bacteria and is actively involved in maintaining host-microbial homeostasis at the gut mucosal interface.

It is documented that a change in diet can alter the degradative activity of the colonic microbiota *in vivo* and in a physiologically relevant setting via influencing the expression of various microbial genes. The complex plant polysaccharides in human diet are not digested and reach the large intestine as potential energy substrates for the gut microorganisms, which harbour a multitude of genes involved in catabolism of carbohydrates. The reduced availability of dietary polysaccharides and fibre can trigger dysbiosis, degradation of the intestinal mucin layer and affecting intestinal health. The gut microbial production of short chain fatty acids and other metabolites has been documented to influence immune system.

The dietary components, thus, influence and alter the composition of the gut microbiome. Various experimental as well as clinical studies have documented the dynamic effect of altering host diet on the microbiota in the gut and other organs, with potential implications for disease modification and treatment depending on inference from gut microbial diagnostics. The present review article aims to highlight that dietary components influence and alter the composition of the gut microbiome.

The human gut microbiosphere

Evolution of microbiome concept: Inside the human body there inhabit trillions of microscopic organisms: bacteria, viruses and archaea, which form the microbiome. The first documented observations about human-associated microbiota were by Antonie van Leeuwenhoek, as early as in 1683 [1]. Later, in 1853, Joseph Leidy published a book entitled A Flora and Fauna within Living Animals, the first important study of the parasites of the alimentary canal [2]. Louis Pasteur, who firmly established causal relationships between microbes, contagion, infection and disease, noted that non-pathogenic microorganisms may have a role in normal human physiology [3]. Later, Escherich noted that understanding the endogenous flora was essential for understanding the physiology of digestion and the pathology and therapy of gastrointestinal diseases [4]. In 1917, Alfred Nissle, held that health-associated microorganisms prevented the establishment of pathogens and propounded the concept of protective microorganism in the gut and colonization resistance [5].

The human gut microbiome

The gastro-intestinal tract, skin and genitals, and various other body organs such as eyes and lungs, harbour large and diverse communities of bacteria, viruses and other microscopic life. The human gut is a nutrient-rich environment and here reside ~ 100 trillion (10^{14}) microbes, the vast majority of which is present in the colon. In the gut ecosystem, microbial organisms inhabit either as residents (autochthonous) or others are derived from food, water and other components of the environment (allochthonous). The adult human gut microbiota is dominated by two main types of bacteria, the *Bacteroidetes* and *Firmicutes*, and an Archaea, *Metanobrevibacter smithii*.

The gut microbes utilize an arsenal of enzymes to utilize available nutrients and have cell-surface molecular apparatus to attach to its habitat, evade bacteriophages and modulate the immune system, genetic framework to mutate, adapt and multiply and avoid annihilation by the immune system and washout. The host-microbial and microbial-microbial relationships, as well as ecologic and eco-genomic perspectives shape the existence and diversity of the gut microbiota [6].

Gut microbiome and metabolism

The gut microorganisms are able to generate thousands of genes which influence the carbohydrate catabolism. Another source of the genetic diversity comes from the concurrent horizontal transfer of genes from to the allochthonous gut bacteria to aid to the ability of bacteria to harvest energy from complex polysaccharides in food. Conversely, in a physiologically relevant setting, the change in diet can affect expression of bacterial genes and alter the degradative activity of the microbiota [7]. Various complex plant polysaccharides are not digested in upper GIT but fermented by a number of anaerobic bacterial species residing in the colon. In addition, certain bacteria such as *Bifidobacterium* and *Bacteroides* species and some bacterial food sources in the host diet can trigger induction of enzymes capable of degrading the intestinal mucin layer to cause dysbiosis and affect adversely the gut health [8].

In a study, mice fed on a fibre-free diet had reduced thickness of the colonic mucosa, which was related to an increased susceptibility to enteric pathogenic bacteria. In another study, the production of short chain fatty acids (SCFAs) by the gut bacteria from complex carbohydrates in dietary fibre, was shown to influence the immune response. The microbial metabolism of dietary components like L-carnitine, as in meat, has been linked to atherosclerosis. There is, thus, a dynamic effect of host diet on the microbiota in the gut and other organs, and potential implication for disease modification and its treatment.

The human gut virome

The human gut virome, is mainly comprised of CrAss-like bacteriophages composed of double-stranded DNA viruses and members of the family Microviridae, which infect the common gut microbes [9]. The human gut virome is, by and large, stable and person specific, and the core gut virome is not shared between adult individuals, as compared to the frequent sharing of the bacterial gut flora [10]. Further, the composition of human gut virome depends on geography, ethnicity and lifestyle [11,12].

Pathophysiological aspects of microbiome

The microbial ecosystems throughout the body have been linked to various aspects of human health. The microbes interact with the molecular processes of the hosts to bring about the physiological changes. There are tentative links between gut microbiota, physical activity and metabolic diseases, mental health and neurological disorders and immune system, allergic disorders and autoimmune diseases. It has been established that the protection from immune disorders is mediated by early-life exposure to commensals bacteria as the beneficial effect of immune-microbial interactions.

Early life microbiota and its influence

The foetus appears to develop in a sterile environment and acquires the bulk of the initial microbiota during and immediately after birth. The first major exposure to microorganisms occurs at birth, being related to the mode of delivery. The vaginally delivered neonates have enriched bacterial flora resembling the maternal vaginal microbiota such as *Lactobacillus* species, whereas the neonates delivered by C-section are richly harbour the skin commensals like *Staphylococcus, Streptococcus* and *Propionibacterium* species [13]. Over time, however, the vaginally born and C-section-born infants gradually reduce the microbial difference. The further acquisition and development of the gut microbiota is influenced by the dietary factors and nutrients. With consumption of complex dietary substrates, there occurs changes in composition of microbiota and associated evolution of microbial functions related to carbohydrate metabolism and

synthesis of biomolecules. With the ongoing evolution, the children acquire a stable microbiota by age of 3 years, which largely resembles that of the adults in the community. The certain postnatal factors are important in development of the microbiota. The human breast milk has a complex community of bacteria which appear seed the infant gut microbiota, dominated by the species that can metabolise oligosaccharides present in the milk [14]. The weaning and diet are major determinant of the gut microbiota as are the environment and people that surround the infant. The genetics also plays a role in the evolution of the determining the microbiota composition, as apparent from the heritability of specific taxa and host genes. In addition, the use of antimicrobials other drugs during early childhood can have impact on the ecological balance of the gut microbiota. Importantly, the microbiota plays a vital role in development of immune, endocrine, metabolic, and other pathways during infancy.

The dysbiosis and its fallouts

The current research has established that there are links between the microbiome and bowel functions, and the altered microbial balance leading to gut dysbiosis, has been correlated to various disease states. The dysbiosis, appears to be a major factor in disorders like inflammatory bowel disease (Figure 1).

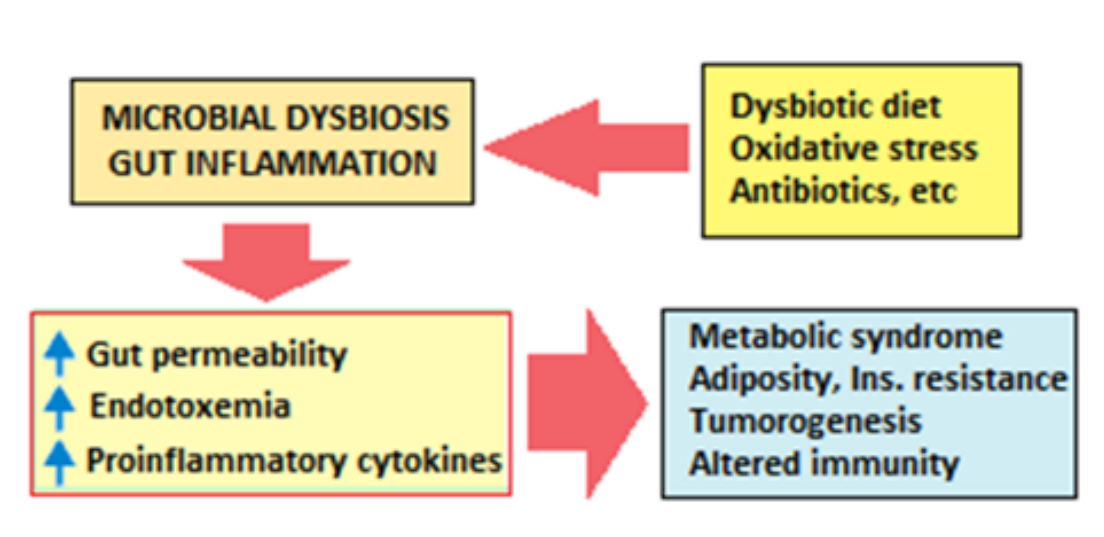

Figure 1: *Pathophysiology and fallouts of microbial dysbiosis.*

The butyrate-producing bacteria such as *Roseburia* and *Lachnospiraceae*, in normal gut cells spurs epigenetic modifications that lead to cell turnover and cell proliferation, while the colorectal cancer patients have a reduced abundance of butyrate-producing bacteria which suppresses cell proliferation and promote cell death. Further, a symbiotic bacterium, *Bacteroides fragilis* protects experimental animals from colitis induced by *Helicobacter hepaticus,* a commensal bacterium with pathogenic potential for polysaccharide A, leading to production of pro-inflammatory cytokines and disease states. The Human Microbiome Project by the National Institutes of Health published, in 2012, the first reference data for microorganisms collected from 242 healthy United States volunteers, covering a number of anatomical sites such as mouth, nose, skin, lower intestine and vagina [15]. It is established that *Bacteroidetes* and *Firmicutes* are the major and *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* are relatively minor constituents of the normal adult gut microbiome [16]. As such, temporarily, the normal human microbiota appears to be variable both within and between individuals.

As per the international MetaHIT (Metagenomes of the Human Intestinal Tract) project, there appears to be an identifiable core microbiome at the gene level rather than the microbial species level [17]. Further, in the gut, commensals are recognized and compartmentalized by IgA secreted in the gut lumen [18]. In the gut ecosystem, the mucosal epithelium remains in direct contact with various microbiota. The Paneth cells from small intestinal epithelial lineage play an important role in sensing enteric bacteria through cell-autonomous MyD88-dependent toll-like receptor (TLR) activation and triggering expression of various antimicrobial factors [19]. The Paneth cells control intestinal barrier penetration by commensal and pathogenic bacteria at the gut mucosal interface. A commensal bacterium can stimulate the antimicrobial peptide production by Paneth cells. Further, at the mucosal interface, these cells actively sense enteric bacteria and play an essential role in maintaining host-microbial homeostasis.

Microbiota in health and disease

The physical activity and microbiome

Exercise, microbiota, and bowel health

Exercise, in general, boosts the levels of gut microbes producing butyrate. In mice experiments, the mice that exercised harboured *Faecalibacterium*, *Clostridium*, and *Allobaculum* in plenty, while the sedentary mice did have in paucity [20]. Further, the exercise in the mice with the high fat diet, prevented weight gain and altered gut microbes, which in sedentary mice was accompanied by gut inflammation [21]. The regular exercise, irrespective of diet or body composition, has been shown to alter the gut microbiota in humans favourably [22]. A recent longitudinal clinical study has documented that in case the sedentary people resorted to regular exercise for six weeks, there occurs increase in levels of microbes like *Clostridiales*, *Lachnospira*, *Roseburia* and *Faecalibacterium* in their guts, and which return back to baseline levels following cessation of exercise [23].

The exercise-gut connection

The bacteria which increase in abundance in the gut following regular exercise, such as *Faecalibacterium* and *Lachnospiraceae* are those which typically produce SCFAs by digesting the dietary fibres. Exercise also appears to change the composition of gut mucus in the gut which influences the bacterial species, such as *Akkermansia muciniphila, which* increases in abundance in response to exercise and has anti-inflammatory properties. In addition, the exercise also modifies the gene expression in the gut immune cells, leading to reduced production of pro-inflammatory cytokines and increased production of anti-inflammatory molecules and antioxidant enzymes. In addition, the intestinal immune cells lying adjacent to the butyrate-producing microbial communities, may produce antimicrobial compounds to retard the growth of other microbial taxa while reinforcing the growth of butyrate-producing microbes [24]. The exercise, also, raises core temperature, increases bile acid circulation and lactic acid level and reduces gut pH and intestinal blood flow. All these factors may potentially alter the gut microbial composition.

Evidence from animal models

The fecal microbiota transplantation studies in mice outline the potential mechanisms of the benefit from exercise [25]. The researchers transplanted the fecal microbiome from mice that exercised and those that did not and into the germ-free mice. The mice with experimentally induced colonic inflammation, when received gut microbes from active donors showed fewer symptoms of inflammatory disease than the mice that received from sedentary inmates through fecal microbiota transplantation (FMT). In another mice study, FMT into obese mice from mice that exercised resulted in reduced weight, fasting blood glucose, and pro-inflammatory cytokines levels [26]. Further, it has been observed that the overweight and obese pregnant female mice, who exercised, transferred beneficial microbes to their offspring.

Gut microbiome and mental health

The clinical studies as well as animal microbial research has established a link between gut microbiota and mental health. There exists a bidirectional microbiota-gut-brain axis, which modulates brain functions and behaviour. It has been found that certain gut microbes and their metabolites influence the brain function, and have been linked to depression, schizophrenia, and other psychiatric disorders. In a study involving schizophrenia patients who were treated for an infection with the antibiotic minocycline, showed improvement in clinical features of psychosis. It was suggested the improvement occurred due to minocycline tamping down inflammation in the brain or knocking down certain gut bacteria or their metabolites influencing the brain function [27].

There is evidence that the butyrate producing *Faecalibacterium*, *Coprococcus* and *Dialister* bacteria are consistently associated with mental health and depleted in depressive illness [28]. The microbial synthesis of the dopamine metabolite 3,4-dihydroxyphenylacetic acid has been correlated with improvement of psychiatric health. Further, there is an evidence to suggest a presumptive link between physical activity level, gut microbial metabolism, and mental health. Other studies have correlated the abundance of certain bacteria, like *Veillonellaceae* and *Lachnospiraceae*, with schizophrenia severity [29]. In the fecal microbiome transplantation studies in mice, the gut microbiome from patients with schizophrenia has been shown to modulate the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviours in mice and levels of glutamate, glutamine, and GABA in their hippocampi. The microbiome, thus, appears to drive changes in the brain that lead to altered behavior. In addition, certain gut microbes produce the neuroactive metabolites or break down the neuroactive compounds in the gut. The *Coprococcus* species is capable of generating 3,4-Dihydroxyphenylacetic acid (DOPAC), a dopamine metabolite associated with depression when depleted.

Microbiota and Intratumor activity

The research in animal models and clinical studies have established a link between the gut microbiota and immune responses to tumor cells [30]. In addition, the microbiota can alter the drugs action through affecting the response to immunotherapy. Further, the gut microbiota can influence the success of anti-malignancy treatment. It appears that some metabolites produced by members of microbiota can alter the immune system's sensitivity to foreign-looking cells that compose tumours. The animal research as well as clinical studies have established a link between the gut microbial composition and immune responses to the tumor cells. The microbial dysbiosis can lead to loss of antitumor immunity.

There is appears to exist a link between the state of the gut microbiota and the response to immunotherapy for a malignancy. Various animal studies in mice indicative of the effect of the state of gut microbiota and the microbial dysbiosis can affect the activity of certain immune cells, such as memory T cells, granulocytes, and monocytes. In a study, Iida., *et al*. have shown that the commensal bacteria may influence the response to CpG-oligonucleotide immunotherapy, which involves short-synthetic segments of DNA, through modulating the tumor microenvironment by secreting tumor necrosis factor (TNF), which in turn can induce tumor necrosis [31].

The bacteria with anti-tumour activity

It has been documented that the colorectal cancer patients have a reduced preponderance of butyrate-producing bacteria like *Roseburia* and *Lachnospiraceae*. It is known that butyrate metabolite in normal cells stimulates epigenetic modifications leading to increased cell turnover and cell proliferation, while in colon cancer cells the fatty acid metabolites seem to suppress cell proliferation and promote cell death.

The research has also documented that mice with melanoma responded better to immunotherapy treatment, such as anti-PD-L1 immune therapy, in presence of a high concentrations of a bacterial taxa *Bifidobacterium* in the gut. When antibiotics were administered to the Ronai's RNF5-knockout mice wiping out the microbial taxa, this specific antitumor response was lost [32]. This leads to an inference

that a course of antibiotics before administering immunotherapy can reduce the desired anti-tumor response. The researchers have noted comparable results when the knockout and wildtype mice were housed together. In the experiments, the knockout mice appear to acquire the microbial taxa from the wildtype mice and showed a suppressed resistance to melanoma activity [33].

The tumours in mice treated with CD8+ T cells, which are programmed to assault the cancer are more likely to shrink if the mice are subjected to prior total body irradiation. This occurs because the radiation damages the fast dividing gut epithelial cells and freeing the commensal microbes elsewhere in the body to secrete the immune-stimulating lipopolysaccharides. If the mice are treated with antibiotics to eradicate the gut microbiota, there occurs enhancement of the T cell function. On the other hand, if antibiotics are given to the nonirradiated mice, there occurs no effect on the efficacy of the T cell function. Thus, it is apparent that the microbes that escaped the gut, influenced the immune response to tumor cells [34].

The bacteria and drug resistance

In a study, it has been found that a bacterium, *Mycoplasma hyorhinis*, which is harboured in the stromal cells, converts gemcitabine, used to treat pancreatic ductal adenocarcinoma, to an inactive form and protects the cancer cells [35]. To prove it experimentally, when the bacteria from the tissue samples were cultured with cancer cell lines, the malignant cells became resistant to gemcitabine.

Microbiota and viral infections including Covid-19

It is known that the microbial ecosystems in various organs interact with the physiological processes linked to immunity. The integrity and normal activity of the gut microbiota, and its coordinated action in relation to defence and immune system are vital for preservation of health as well as protection from various diseases and bacterial and viral infections [36]. Certain metabolites or other molecules produced by members of the microbiome alter the immune system's sensitivity and effectivity to viral infections, thus, helping to promote viral evasion of certain viruses by direct and indirect mechanisms to increase infection and viruses using LPS and surface polysaccharides from bacteria to trigger immunosuppressive pathways [37]. In addition, the gut microbial enzymes and secreted molecules influence absorption, metabolism, efficacy, and toxicity of drugs used in viral infections. Thus, there is a causal relationship between altered microbial communities, i.e. dysbiosis, immune response and disease including viral infections like Covid-19 (Figure 2).

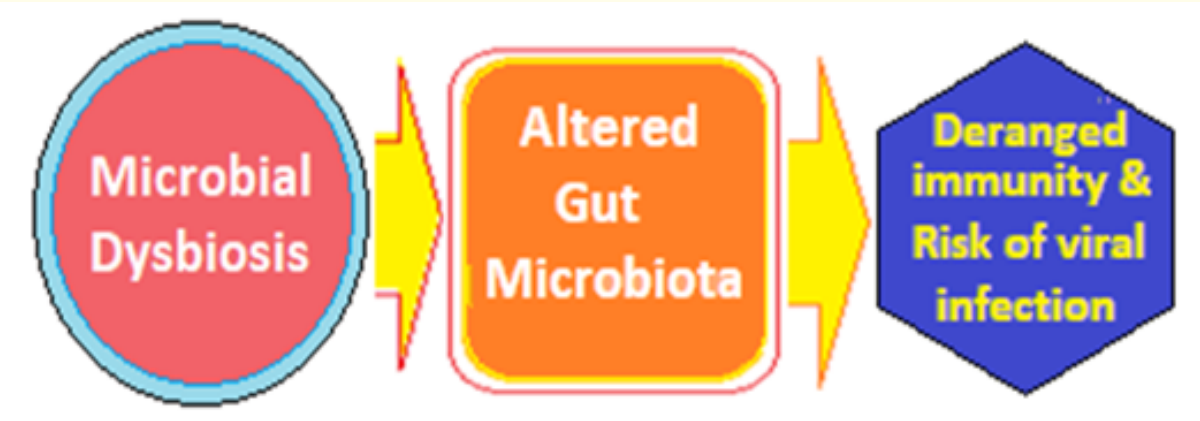

Figure 2: *The basis of probiotic treatment in viral infections.*

During the in course of infection process, various viruses encounter and interact with the host's commensal microbiota, and in the regulation of viral infection, commensal microbiota appears to play a variable but critical role [38]. Through diverse mechanisms, the microbiota exerts substantial inhibitory effects on viral infection. In addition to fostering the generation of immunoregulatory Treg cells, the commensal microbiota has antiviral effect by enhancing the activation of effector immune cells and the production of various inflammatory cytokines that are pivotal for virus elimination. On the other hand, microbiota may promote viral infections as the commensal microbiota may facilitate genetic recombination of viruses and enhance their infectivity.

It has been shown that the gut microbiota has a stimulatory or suppressive role in viral infections [39]. The gut microbiome may modulate the viral replication, transmission and persistence, and viral elimination. The microbiota, in turn, is influenced by the invading viruses through various mechanisms and its integrity can be disrupted by invading viruses leading to microbial dysbiosis in the host and promoting the virus infectivity [40].

Microbiota and drug action

Through their effects on drug absorption and metabolism, the gut microbiota affects efficiency of medication. The enzymes and metabolites produced by gut microbes can influence the activation of a pro-drug. In addition, there is an enormous influence of microbiota on human physiology. The resident commensal bacteria in human gut produce much more circulating metabolites and other molecules than produced by the different cells taken together. As far as the metabolism of host-directed drugs is concerned, about two-thirds of the more than 276 drugs incubated with about 76 human gut bacterial species have been shown to be modified by the gut microbes [41]. Further, various studies have confirmed the role of the microbiota in the gut and elsewhere, in drug metabolism, efficacy, and toxicity. The microbiota has been linked with the efficacy of drugs for a wide range of conditions and shown to affect the metabolism of drugs ranging from the anti-epileptic, zonisamide and hormonal preparations like insulin and calcitonin. Given the microbiome's wide-ranging effects, the interplay between microbiota and drugs has the potential to transform the practice of medical therapeutics.

Peppercorn and Goldman demonstrated three decades earlier that the anti-inflammatory drug, salicylazo-sulfapyridine, degraded in wild mice and when cultured with human gut bacteria, but not in germ-free mice. The experiments outlined a role for the gut microbiota in drug metabolism [42]. The bacterial product, p-cresol sulphate, can influence the rate at which human metabolize acetaminophen, a common analgesic. The mechanism of these effects has been related to the actions of bacterial products on the drugs [43]. The gut microbes are known to produce an enzyme, tyrosine decarboxylase which can convert the pro-drug L-dopa into dopamine, the active drug which is able to cross the blood-brain-barrier and, thus, the abundance of the bacterial taxa to produce tyrosine decarboxylase has been correlated with the required dose of L-dopa. This can also help explain differences in efficacy of L-dopa among individuals [44]. Another study has identified a small-molecule inhibitor that appear blocks the action of tyrosine decarboxylase in mice [45]. Certain bacterial species may enhance the efficacy of a drug as seen with the cholesterol-lowering statin, which correlates with blood levels of the secondary bile salts produced by gut bacteria from the bile acids, both sharing transporter proteins in the liver and intestine. The mice treated with the cholesterol-lowering drug lovastatin interact with antibiotics therapy [46].

Modifying microbiota with nutraceuticals

The current research has established a causal relationship between altered microbial communities and disease.

The intestinal dysbiosis is known factor having impact on various disease states [47]. The extra-intestinal disorders associated with gut microbiota have been found in previously unexpected areas, including metabolic diseases, neuropsychiatric disorders, autoimmune diseases, allergic disorders, viral infections, and tumours. A randomized controlled trial showed improved insulin sensitivity, along with increased levels of butyrate-producing intestinal microbiota. There are case reports of FMT having favourable outcomes with microbiota

intervention through dietary interventions, nutraceutical therapy and fecal microbiota transplantation in diabetes, Parkinson's disease, multiple sclerosis, chronic fatigue syndrome, and idiopathic thrombocytopenic purpura [48].

The gut dysbiosis appears to be a major factor in disease states like inflammatory bowel disease. A symbiotic bacterium, *Bacteroides fragilis* has been shown to protect experimental animals from colitis induced by *Helicobacter hepaticus,* a commensal bacterium with pathogenic potential through polysaccharide A (PSA). The purified PSA administered to animals suppressed pro-inflammatory interleukin-17 production by intestinal immune cells and also protects from inflammatory disease [49]. The studies indicate that certain nutraceuticals may provide clinical relief in patients infected with encapsulated RNA viruses such as influenza and Covid-19. These nutraceuticals have been shown to reduce the inflammation in various organs including lungs and help to enhance type 1 interferon response to the viral infections including coronavirus [50]. The various nutraceuticals and their active ingredients, having therapeutic effect include Ferulic acid, Lipoic acid, *Spirulina, Siberian ginseng, Echinacea purpurea*, N-Acetylcysteine, Selenium, Glucosamine, Zinc, Yeast Beta-Glucan and Elderberry [51]. The nutraceuticals appear to reduce the duration of the disease and clinical severity of the infection as well as mortality in experimental animals infected with influenza virus [52]. Selenium is a cofactor for various peroxidases and its deficiency leads to malfunctioning of certain physiological processes, which enhances the rate of virus mutation and promotes evolution of resistant and more pathogenic strains. The zinc ion is helpful in proliferation and function of immune cells.

Conclusion: Impact of Nutritive Support

The nutrients and nutraceuticals

The change in diet can alter the degradative activity of the colonic microbiota in a physiologically relevant setting due to altered expression of bacterial genes [53]. Most of the complex plant polysaccharides are not digested and fermented by a variety of anaerobic bacteria such as *Bifidobacterium* and *Bacteroides* species, other microbials resident in the colon use the undigested polysaccharides as a potential food source for their metabolism. These gut microorganisms carry genes required in catabolism of carbohydrates. In addition, a potential source of genetic diversity is horizontal transfer of genes from environmental microorganisms to gut bacteria, which is able to alter the ability of bacteria to harvest energy from indigestible polysaccharides in the food. These bacterial strains can trigger induction of enzymes capable of degrading the intestinal mucin layer in case of sparse fibre intake, affecting intestinal health and causing dysbiosis [54]. The nutrients influence the properties of gut microbiota and able to keep a flexible network of genes by the differential expression of bacterial enzymes (Figure 3).

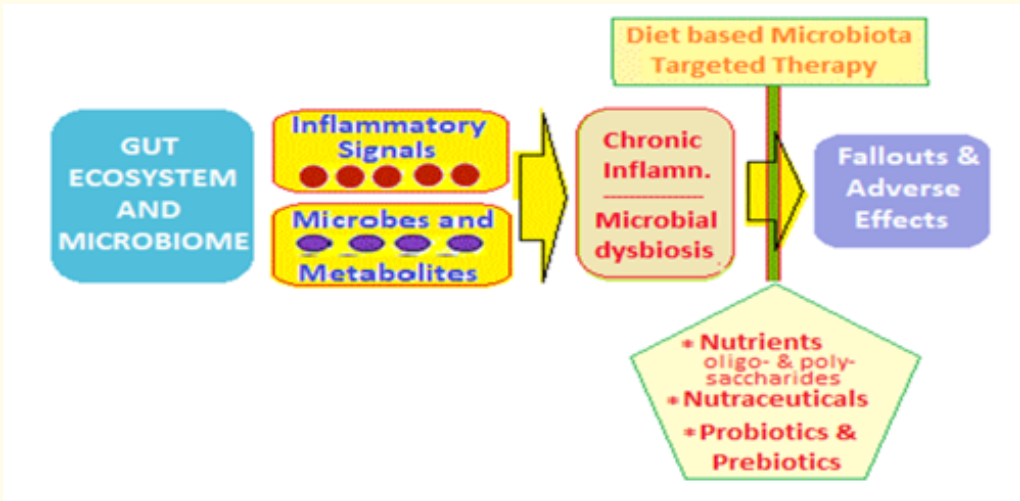

Figure 3: *Nutrients, nutraceuticals and probiotics based therapy for dysbiosis.*

The low fibre diets are harmful, as evidenced by a mice study, in which the fibre-free diet reduced the thickness of their colonic mucus layer, and increased susceptibility to disease caused by a mouse enteric pathogen [55]. In another study, the microbial production of SCFAs from digestion of dietary fibre altered the immune response in mouse suffering from lung disease [56]. There are indications from studies that the microbial metabolism of dietary components, such as L-carnitine in meat, may be linked to enhanced atherosclerosis [57]. The studies, thus, highlight the potential and dynamic effect of diet on the microbiota in the gut and other organs, which may have therapeutic implications for disease modification and treatment.

The role of prebiotics and probiotics

There are beneficial probiotic bacteria, which positively modulate immune response and promote the host defence. The common probiotics include *Lactobacillus* or *Bifidobacterium* species, non-pathogenic forms of *Escherichia coli* and *Bacteroides* and yeasts like *Saccharomyces*. The lactic acid bacteria (LAB) has shown antibacterial as well as antiviral activity against various viruses [58]. The Lactococcus lactis strain Plasma (LC-Plasma) possesses strong stimulatory activity for plasmacytoid dendritic cells to inhibit viral replication control via TLR9-pathway [59].

The probiotics use in viral infections appear to activate recognition of the virus and bonding of receptors and its domains on the host cells. The probiotics can suppress the replication of virions and improve the host immune response. The immunomodulatory effect of specific probiotics seems to be strain-specific and involve a combination of signaling pathways, which are activated following interactions between specific microbe-derived ligands, corresponding pattern recognition receptors and domains on host cells. In general, the probiotics appear to induce changes in dendritic cells, T-cells, natural killer cells, and alveolar macrophages, which form the basis of the protective effect of probiotics.

It has been documented that the probiotic bacteria as well as their components are able to induce potentially beneficial effects in the host cells, also [60]. The probiotic bacteria synthesize compounds like lactic acid, acetic acid and γ-aminobutyric acid, which play a role in improving host immunity and regulating sepsis [61]. Further, the probiotic bacteria secrete compounds like exopolysaccharides (EPSs) are long-chain polysaccharides that may improve levels of IFN-ϫ, IL-6, IL-8 and inhibit viral infection [62].

Bibliography

1. Wollman AJ., *et al.* "From Animaculum to single molecules: 300 years of the light microscope". *Open Biology* 5.4 (2015): 150019.

2. Hare H A. "Leidy and His Influence on Medical Science". *Proceedings of the Academy of Natural Sciences of Philadelphia* 75 (1923): 73-87.

3. Casanova JL and Laurent A. "The Genetic Theory of Infectious Diseases: A Brief History and Selected Illustrations". *Annual Review of Genomics and Human Genetics* 14 (2013): 215-243.

4. Falk PG., *et al.* "Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology". *Microbiology and Molecular Biology Reviews* 62.4 (1998): 1157-1170.

5. Sassone-Corsi M and Raffatellu M. "No Vacancy: How beneficial microbes cooperate with immunity to provide colonization resistance to pathogens". *Journal of Immunology* 194.9 (2015): 4081-4087.

6. Ley RE., *et al.* "Ecological and Evolutionary Forces Shaping Microbial Diversity in the Human Intestine". *Cell* 124.4 (2006): 837-848.

7. Xu J and Gordon JI. "Honor thy symbionts". *Proceedings of the National Academy of Sciences of the United States of America* 100.18 (2003): 10452-10459.

8. Wilson BA., *et al.* "Bacterial Pathogenesis: A Molecular Approach, 3rd Edition". AMS Science (2011).

9. Scarpellini E., *et al.* "The human gut microbiota and virome: Potential therapeutic implications". *Digestive and Liver Disease* 47.12 (2015): 1007-1012.

10. Beller L and Matthijnssens J. "What is (not) known about the dynamics of the human gut virome in health and disease". *Current Opinion in Virology* 37 (2019): 52-57.

11. Minot S., *et al.* "The human gut virome: inter-individual variation and dynamic response to diet". *Genome Research* 21.10 (2011): 1616-1625.

12. Shkoporov A., *et al.* "The human gut virome is highly diverse, stable, and individual specific". *Cell Host Microbe* 26.4 (2019): 527-541. e5.

13. Milani C., *et al.* "The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota". *Microbiology and Molecular Biology Reviews* 81.4 (2017): e00036-e000317.

14. Marcobal A., *et al.* "Consumption of Human Milk Oligosaccharides by Gut-related Microbes". *Journal of Agricultural and Food Chemistry* 58.9 (2010): 5334-5340.

15. Peterson J., *et al.* "For the NIH HMP Working Group. 2009. The NIH Human Microbiome Project". *Genome Research* 19.12 (2009): 2317-2323.

16. Proctor L., *et al.* "A review of 10 years of human microbiome research activities at the US National Institutes of Health, Fiscal Years 2007-2016". *Microbiome* 7 (2019): 31.

17. Qin J., *et al.* "A human gut microbial gene catalog established by metagenomic sequencing". *Nature* 464.7285 (2010): 59-65.

18. Harris NL., *et al.* "Mechanisms of neonatal mucosal antibody protection". *Journal of Immunology* 177.9 (2006): 6256-6262.

19. Vaishnava S., *et al.* "Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface". *Proceedings of the National Academy of Sciences of the United States of America* 105.52 (2008): 20858-20863.

20. Matsumoto M., *et al.* "Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum". *Bioscience, Biotechnology, and Biochemistry* 72.2 (2008): 572-576.

21. Allen JM., *et al.* "Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically induced colitis in gnotobiotic mice". *Gut Microbes* 9.2 (2018): 115-130.

22. Sergeev IN., *et al.* "Effects of Synbiotic Supplement on Human Gut Microbiota, Body Composition and Weight Loss in Obesity". *Nutrients* 12.1 (2020): 222.

23. Monda V., *et al.* "Exercise Modifies the Gut Microbiota with Positive Health Effects". *Oxidative Medicine and Cellular Longevity* (2017): 3831972.

24. Mailing LJ., *et al.* "Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health". *Exercise and Sport Sciences Reviews* 47.2 (2019): 75-85.

25. Lai ZL., *et al.* "Fecal microbiota transplantation confers beneficial metabolic effects of diet and exercise on diet-induced obese mice". *Scientific Reports* 8 (2018): 15625.

26. Wang PX., *et al.* "Gut microbiota and metabolic syndrome". *Chinese Medical Journal* 133.7 (2020): 808-816.

27. Solmi M., *et al.* "Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia". *CNS Spectrums* 22.5 (2017): 415-426.

28. Valles-Colomer M., *et al.* "The neuroactive potential of the human gut microbiota in quality of life and depression". *Nature Microbiology* 4 (2019): 623-632.

29. Zheng P., *et al.* "The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice". *Science Advances* 5.2 (2019): eaau8317.

30. Vivarelli S., *et al.* "Gut Microbiota and Cancer: From Pathogenesis to Therapy". *Cancers (Basel)* 11.1 (2019): 38.

31. Iida N., *et al.* "Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment". *Science* 342.6161 (2013): 967-970.

32. Sethi V., *et al.* "Gut Microbiota Promotes Tumor Growth in Mice by Modulating Immune Response". *Gastroenterology* 155.1 (2018): 33-37.

33. Parker KD., *et al.* "Microbiome Composition in Both Wild-Type and Disease Model Mice Is Heavily Influenced by Mouse Facility". *Frontiers in Microbiology* 9 (2018): 1598.

34. Paulos CM., *et al.* "Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling". *Journal of Clinical Investigation* 117 (2007): 2197-2204.

35. Geller Lt and Straussman R. "Intratumoral bacteria may elicit chemoresistance by metabolizing anticancer agents". *Molecular and Cellular Oncology* 5.1 (2018): e1405139.

36. Christopher M., *et al.* "Viruses and the Microbiota". *Annual Review of Virology 1* (2014): 55-69.

37. Domínguez-Díaz C., *et al.* "Microbiota and Its Role on Viral Evasion: Is It With Us or Against Us?". *Cellular and Infection Microbiology* 9 (2019): 256.

38. Yaron JR., *et al.* "Immune protection is dependent on the gut microbiome in a lethal mouse gamma herpes viral infection". *Scientific Reports* 10 (2020): 2371.

39. Groves HT., *et al.* "Respiratory Viral Infection Alters the Gut Microbiota by Inducing Inappetence". *mBio* (2020).

40. Li N., *et al.* "The Commensal Microbiota and Viral Infection: A Comprehensive Review". *Frontiers in Immunology* 10 (2019): 1551.

41. Zimmermann M., *et al.* "Separating host and microbiome contributions to drug pharmacokinetics and toxicity". *Science* 363 (2019): eaat9931.

42. Peppercorn MA and Goldman P. "The role of intestinal bacteria in the metabolism of salicylazosulfapyridine". *Journal of Pharmacology and Experimental Therapeutics* 181 (1972): 555-562.

43. Clayton TA., *et al.* "Pharmacometabolomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism". *Proceedings of the National Academy of Sciences of the United States of America* 106 (2009): 14728-14733.

44. Van Kessel SP., *et al.* "Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease". *Nature Communications* 10. 310 (2019).

45. Rekdal V M., *et al.* "Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism". *Science* 364 (2019): 6445.

46. Yoo DH., *et al.* "Gut microbiota-mediated drug interactions between lovastatin and antibiotics". *Drug Metabolism and Disposition* 42 (2014): 1508-1513.

47. DeGruttola AK., *et al.* "Current understanding of dysbiosis in disease in human and animal models". *Inflammatory Bowel Disease* 22.5 (2016): 1137-1150.

48. Xu MQ., *et al.* "Fecal microbiota transplantation broadening its application beyond intestinal disorders". *World Journal of Gastroenterology* 21.1 (2015): 102-111.

49. Mazmanian SK., *et al.* "A microbial symbiosis factor prevents intestinal inflammatory disease". *Nature* 453 (2008): 620-625.

50. McCarty MF and DiNicolantonio JJ. "Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus". *The Journal of Arthroplasty* 35.7 (2020): S49-S55.

51. Hawkins J., *et al.* "Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials". *Complementary Therapies in Medicine* 42 (2019): 361-365.

52. Humpherys B and Busath DD. "Anti-Influenza Nutraceuticals: Antiviral and Anti-Inflammatory Effects". *Advances in Complementary and Alternative Medicine* 4.2 (2019).

53. Xu J and Gordon JI. "Honour thy symbionts". *Proceedings of the National Academy of Sciences of the United States of America* 100.18 (2003): 10452-10459.

54. Wilson BA., *et al.* "Bacterial Pathogenesis: A Molecular Approach, 3rd Edition". AMS Science (2011).

55. Desai MS., *et al.* "A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility". *Cell* 167.5 (2016): 1339-1353.e21.

56. Lewis G., *et al.* "Dietary Fiber-Induced Microbial Short Chain Fatty Acids Suppress ILC2-Dependent Airway Inflammation". *Frontiers in Immunology* 10 (2019): 2051.

57. Koeth RA., *et al.* "Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis". *Nature Medicine* 19.5 (2013): 576-585.

58. Maeda N., *et al.* "Oral administration of heat-killed lactobacillus plantarum l-137 enhances protection against influenza virus infection by stimulation of type I interferon production in mice". *International Immunopharmacology* 9 (2009): 11-22.

59. Horie A., *et al.* "Characterization of genomic DNA of lactic acid bacteria for activation of plasmacytoid dendritic cells". *BMC Microbiology* 19 (2019): 88.

60. O'Toole PW., *et al.* "Next-generation probiotics: the spectrum from probiotics to live biotherapeutics". *Nature Microbiology* 2 (2017): 17057.

61. Nikhra V. "The Gut Microbial Dysbiosis, its Fallouts and Redressal". *Advances in Nutrition and Food Science ANAFS* (2019): 123.

62. Li N., *et al.* "The Commensal Microbiota and Viral Infection: A Comprehensive Review". *Frontiers in Immunology* 10 (2019): 1551.

Volume 4 Issue 9 September 2020