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The Need And The Methods Of Human Microbiome Modulation: A Review

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Abstract

Introduction: Unani system of medicine is an exquisite & holistic system of healthcare which, not only promises the complete cure of various ailments but also offers standard regimes for health promotion, disease prevention and rehabilitation. These regimens encompass various dietary recommendations, life style modifications and certain disease specific therapies. Although the treasure of ancient Unani medical writings suggests enough indications and therapies for meet most of the common ailments, yet to meet the emerging challenges in healthcare sector, new methods need to be explored and introduced into the Unani system to ensure efficient services. Therefore, this study the "Introducing Human Microbiome Modulation in Unani Medicine: The Need and the Methods of Intervention" was conducted in the PG department of Munafeul Aza, Ajmal Khan Tibbiya College, AMU, Aligarh with the following aims and objectives:

Objectives of the Study:

1. To compile various descriptions on Human Microbiome from authentic literary resources,
2. To review the need and the methods of Human Microbiome Modulation and
3. To propose the adoption of the methods of Human Microbiome Modulation in Unani therapeutics.

Study design: Descriptive research study
Procedure: review of various literary sources Manuscript, Books, Journals, Web, eBooks etc. on the topic available online and offline. The relevant information was compiled to draw inference and conclusion was presented.
Conclusion: after thorough review of various manuscripts, books, papers and journals it can be concluded that the concept of Human Microbiome Modulation holds important place in healthcare practices. This method can easily be adopted by Unani Scholars for holistic healthcare of the patients. The details are discussed below.

Keywords: Unani Medicine, Holism, Human Microbiome Modulation**,** prebiotics, probiotics, fecal microbial transplantation (FMT)

Introduction and Need for the Study: The human microbiome has long been of research interest due to their importance to human health, nutrition, and well-being. Gut microbiome can be defined as the microorganisms inhabitant in the gastrointestinal tract including bacteria, viruses, protozoa, and fungi and their collective genetic material present within it. A healthy gut microbiota is normally required for human health to maintain host immune homeostasis including skin, nutrient intake, as well as gut development. An unbalanced gut microbiota or dysbiosis in microbes often leads to occurrence of both acute and chronic diseases, such as infectious diarrhoea, inflammatory bowel diseases, obesity, diabetes, colon cancer, and neonatal necrotizing enterocolitis; not only metabolism-related disease, but also skin diseases like acne vulgaris and atopic dermatitis, in addition to psychological problems such as depression and autism[1]. The human microbiome modulation is recently recognised as an important tool of healthcare. James M Kinross et. al. highlighted the significance of understanding gut microbiome activity in relation to human health and the potential for gut microbial modulation in disease treatment[2]. Douglas Allan Leach et. al. found that microbiome diversity predicted surgical success in patients with rectovaginal fistula, suggesting the potential for personalized healthcare strategies based on microbiome analysis[3]. Rajbardhan M. et. al. emphasized the role of the microbiome in metabolic and immunologic modulation, particularly in carcinogenesis and tumor development, using germ-free animal models[4]. Bin Hu et. al. explored the effects of fecal microbiota transplantation on depression, highlighting the therapeutic potential of microbiome modulation in mental health[5]. Similarly, Holly N Wilkinson et. al proved that the selective depletion of staphylococcus aureus restores the skin microbiome and accelerates tissue repair after injury[6]. Moreover, Ehsan Amini-Salehi et. al. explored the relationship between gut microbiome modulation and blood pressure in type 2 diabetes[7]. All these studies point towards the merging research potential in the field of human microbiome. All healthcare systems including Unani system of medicine can serve humanity in better way with due additions of updated knowledge and skills. Four core modes of treatment are usually employed in Unani medicine such as ‘ilāj bi’l-tadbīr (regimenal therapy), ‘ilāj bil ghizā (dietotherapy), ‘ilāj bi’l-dawā’ (pharmacotherapy) and ‘ilāj bi’l-yad (surgery)[8]. Microbiome modulation may find an important place among these modes of treatment. Therefore, for understanding the need, benefits and the methods of microbiome modulation, this work was done in the department of Tashreeh wa Manafeul Aza, Ajmal Khan Tibbia College, AMU,Aligarh. The aims and objectives of the study were as follows:

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Literature review:

Human microbiome: The human microbiome is the aggregate of all microbiota that reside on or within human tissues and biofluids[9].

The human microbiota is defined as a set of organisms inhabiting and interacting with the human body[10].

The origin of “microbiota” is dated back to early 1900s. It represents a vast number of microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body (gut, skin, lung, oral cavity)[11].

Although “microbiota” and “microbiome” are often interchangeable, there are certain differences between the two terms. Microbiota describes the living microorganisms found in a defined environment, such as oral and gut microbiota. Microbiome refers to the collection of genomes from all the microorganisms in the environment, which includes not only the community of the microorganisms, but also the microbial structural elements, metabolites, and the environmental conditions.[12]

Physiological functions of human microbiome:

1. **Protection against pathogens**: In the state of balance and harmony in the composition and function of human microbiome (eubiosis), the dominant, non-pathogenic gut microorganisms grow in specific niches and play a suppressive role in pathogenic colonization and growth[13].

2. **Development of Immune System:** The gut microbiome stimulates and contributes to the maturation of the immune system in response to pathogens, and this step is important to induce and sustain tolerance[14].

3. **Digestion and metabolism:**

The gut microbiome aids in the digestion of complex carbohydrates and the synthesis of essential vitamins. It also influences metabolic processes, contributing to energy balance and nutrient absorption[15].

The gut microbiota makes an important contribution to human metabolism by contributing enzymes that are not encoded by the human genome, for example, the breakdown of polysaccharides, polyphenols and synthesis of vitamins[16].

The major function of the gut microbiota are in digestion and nutrient utilization. The gut microbiota manufacture short chain fatty acids (SCFAs) from dietary fiber digestion via the saccharolytic pathway, which is responsible for the majority of microbiota-generated SCFAs. They also break down protein via the proteolytic pathway, which also produces SCFAs and other metabolites such as ammonia, thiols, and various amines. The SCFAs obtained from the digestion of complex carbohydrates perform several roles and are mainly butyrate, propionate, and acetate. Butyrate is vital in glucose homeostasis and energy regulation. Acetate helps in fat storage regulation, while propionate acts as a raw material for gluconeogenesis in the liver. These SCFAs can be interchanged by the microbiota based on a particular SCFA demand. Gut bacteria can also change bile acid composition and affect host metabolism. They produce secondary bile acids from unabsorbed primary bile acids. The secondary bile acid finds its way into the host blood system, where it modifies the pathways that are responsible for metabolism, inflammation, and energy balance. Gut microbiota operates as a pseudo-organ with unparalleled endocrine potential. They produce plenty of regulatory chemicals via metabolism-independent or metabolism-dependent pathways, in comparison with the host endocrine organs that liberate a few hormones[17].

4. **Synthesizing Essential Nutrients:**

In humans it has been shown that members of the gut microbiota are able to synthesize vitamin K as well as most of the water-soluble B vitamins, such as biotin, cobalamin, folates, nicotinic acid, panthotenic acid, pyridoxine, riboflavin and thiamine[18].

5. **Breaking down Potentially Toxic Compounds:**

Gut microbes also modify the chemical structures of numerous ingested, foreign compounds (xenobiotics), including dietary components, environmental pollutants, and pharmaceuticals. Such transformations were identified as early as the 1950s in humans, animal models, fecal samples, and individual microbes[19].

Microbiota stimulate the immune system, break down potentially toxic food compounds, and synthesize certain vitamins and amino acids including the B vitamins and vitamin K[20].

6. **Regulating Immune Function:**

When the normal functions and crosstalk between the microbiome and gut barrier are disrupted, an aberrant immune-inflammatory response is generated. Potential consequences include inflammation, allergy, and autoimmune disorders mediated by molecular mimicry and abnormal T-cell response[21].

The interest in the potential modulation of the microbiome and the use of probiotics to prevent dysbiosis or to cure gut microbial abnormalities is gaining popularity within the scientific community, given the fact that the gut microbiome has been implicated in several diseases including obesity, cardiovascular diseases, hypertension, cancer, inflammatory bowel disease, and several others[22].

Microbiome modulation

Microbiome modulation is defined as an intervention with the intent of pushing the gut microbiome toward a desired state. This includes, among others, fecal microbiota transplantation, probiotic and prebiotic treatment, and directed dietary interventions[23].

The Need of Microbiome Modulation:

Microbiota manipulation represents a significant opportunity for changing global health practices. The problems related to standardization, optimization, security and supervision should be solved. The microbiota modulation can optimize healthcare and promote worldwide health[24].

Modulation of microbiome is intended to intervene in the symptomatology or causes of diseases in order to improve health status[25]. The prebiotic effect in gut can be assessed by decreasing intestinal pathogens, increasing production of metabolites related to the activity of beneficial bacteria, decreasing toxic metabolites and for the effect on the microbiome structure[26].

Methods of Microbiome Modulation:

Microbiota has several mechanisms through which it can be modulated; natural, induced, or engineered. These methods include:

1. Dietary interventions
2. Fecal microbiota transplantation (FMT)
3. Antibiotic therapy
4. Environmental factors
5. Microbiome engineering
6. Phage therapy
7. Microbiota-targeted drug development
8. Microbiota-directed prodrugs

1. **Dietary interventions:**

   Gut microbiota plays a fundamental role within human health, and exerts key functions within the human body. Diet is one of the most powerful modulators of gut microbiota functions and composition. This complex interplay involves also the immune system and the intestinal barrier, highlighting the central role of diet in the pathogenesis and treatment of multiple diseases.

   Prebiotics: These are not digestible dietary components with examples like fiber inulin and oligosaccharides that stimulate selectively growth and/or activity of good bacteria inside the gut. They act as specific microbes' substrates thereby enhancing their proliferation and metabolic activity[27].

Probiotics: Live microorganisms that on consumption at adequate levels confer a benefit on health. Probiotic sources include fermented foods such as yogurt or kimchi or they can be taken as supplements. They introduce beneficial species directly into the gut microbiota or affect the activity patterns of existing populations within it.

Synbiotics: are combinations of prebiotics and probiotics which have synergistic effects on the gut microbiota. In the gut, prebiotics provide food for probiotics thus hiking up their presence and activity[28].

2. **Fecal microbiota transplantation (FMT):**

FMT is where fecal material is taken from a healthy donor and given to someone whose microbiota has been disrupted or become unhealthy as a result of disease. Despite being mainly used for recurrent Clostridioides difficile infections, FMT also looks into other conditions linked with dysbiosis like metabolic disorders, and inflammatory bowel disease (IBD). FMT brings back the diversity of microorganisms in an individual's intestine hence promoting better health outcomes[29].

3. **Antibiotic therapy:**

Antibiotics are meant mainly to kill pathogenic bacteria, they can have considerable impacts on commensal microbiota. Antibiotics may result in dysbiosis when susceptible species are killed or it may change the balance between different microbial taxa. Dysbiosis following such disruptions increases vulnerability to opportunistic infections and other diseases related to microbiome disturbance. Yet at times, antibiotics can be exploited intentionally to influence the composition of microbiota, such as small intestinal bacterial overgrowth or specific depletion of pathogens[28].

Bacteriophages are also known as bacterial viruses which invade and multiply in bacteria. They serve as natural predators of bacteria that form microbial communities and play an important role in determining the population. The phage therapy aimed at curing the bad things in microbial, one of the possible directions regarding the modulation of microbiota is being considered. Phage therapy shows promise as an effective treatment, especially with the capacity to eradicate harmful bacteria while still preserving beneficial indigenous microbiota present in different environments such as the human body[29].

4. **Environmental factors:**

Several environmental variables have been put forward to influence the composition and function of microbial communities, including stress, pollution, dietary changes, and lifestyle. Since the factors that shape microbiota are very crucial to understanding how these processes lead to changes in the microbiome, it is important to understand them to solve them using appropriate measures. For instance, direct effects may be produced by environmental pollutants or dietary components on the growth and metabolism of microorganisms leading to changes in compositional traits and activity of microbiota[29].

Immune System Modulation:

The host immune system helps in the development of an active microbiota and also guides the composition and functions of different structures. Indirectly, the immunomodulatory therapeutics impact on microbiota and their hosts; with immunosuppressants or immunostimulant types. For instance, modulation of the gut immune system through dietary components or pharmacological agents influences the composition of gut microbiota while one way or another it is also influenced by way of composition of the same[28].

Microbial Interactions:

Within a community, microorganisms can interact with each other in different ways such as through competition whereby some organisms feed on others thus supporting the reproduction of these species. Thus, comprehension of these microbial relationships is mandatory for providing an opportunity to predict how e given intervention affecting the modulation of the microbiota affects structure and functionality in general. For instance, a newly introduced phototrophic microbial species in the eco-system of the microbiota through probiotics or phage therapy might lead to ecological changes that affect other community members[29].

Host-Microbe Crosstalk:

The messages circulating along various signalling pathways enable two-way communication between the host and its associated microbiota. These interactions, facilitated by host-derived molecules as well as contents and microbial metabolites discussed are key to the host homeostasis and how it affects the microbe's Kingdom. There are many ways to consider host-microbe crosstalk either through dietary interventions, microbial therapies, or host-targeted therapies; modifications in the composition and functions of microbiota shall also be possible[28].

Ecological Principles: Secondly, microbial communities operate on advanced ecological rules that include niche separation, succession, and resilience. Considering these ecological principles is essential to devising balanced approaches toward modulating the microbiota. For instance, in the case of rebuilt microbial diversity or stabilized ecosystems, the interventions improve perturbation tolerance and support for long-term equilibrium between the microbiota. Microbiota modulation mechanisms are dynamic and complex, as they involve various dietary interventions, microbial therapies, ecological principles, and host-pathogen activity. Microbiota modulation is effective when this body of knowledge is fully developed and targets microbiota across localized environmental conditions has the body in human beings, agricultural systems, or natural surroundings[29].

5. **Microbiome engineering:**

Under this approach, microbial communities are deliberately influenced or triggered through the solutions and techniques of synthetic biology. It includes methodologies like designing probiotic bacteria to transmit curative molecules or manipulating microbial consortia with distinctive roles. The great potential of engineering the microbiome allows us to develop precise and controlled interventions that modulate microbial nutrients or species for a range of uses, such as disease control, and environmental remediation, among other bioproduction applications[28].

6. **Phage therapy:**

Bacteriophage Engineering

Advances in phage isolation, characterization, and genetic engineering offer opportunities to develop customized phage cocktails targeting specific pathogenic bacteria while preserving the native microbiota. Future research may focus on elucidating phage-host interactions, optimizing phage delivery methods, and overcoming challenges related to bacterial resistance and phage pharmacokinetics.

Phage-Mediated Modulation of Microbiota

Beyond pathogen eradication, phages can modulate the composition and function of the microbiota. Future studies may explore the use of phages to selectively target and manipulate key microbial species involved in dysbiosis-associated diseases, such as IBD, obesity, and allergic disorders[30].

7. **Microbiota-targeted drug development:**

Novel therapeutics designed to modulate the microbiota composition or activity hold promise for treating various diseases. Future drug development efforts may involve screening natural compounds, small molecules, and biologics for their microbiota-modulating effects and optimizing their pharmacokinetic properties for clinical use[30].

8. **Microbiota-directed prodrugs:**

Prodrugs that require microbial metabolism for activation represent an innovative approach for site-specific drug delivery and enhanced therapeutic efficacy. Future research may explore the design and optimization of microbiota-directed prodrugs for targeted treatment of gastrointestinal disorders, infections, and systemic diseases. Future research directions in microbiota modulation encompass a diverse array of approaches, ranging from microbial-based therapies and phage therapy to microbiome engineering and microbiota-targeted drug development. Continued innovation in these areas holds the potential to revolutionize healthcare by harnessing the therapeutic potential of the human microbiome[24].

Discussion:

Among the various thrust areas of research and innovation in the field of healthcare; the human microbiome finds a significant place. Seeing the importance of the impact of the research outcomes on human health; human microbiome modulation was taken up for an extensive critical review in the department of Tashreeh wa Manafeul Aza, of a unani college of an Indian central university. During this study, it was intended to review the concept of Human Microbiome and its physiological functions along with the need and methods of microbiome modulation known so far. keeping an eye on these aims, an extensive literature review of various resources available online and offline was done. The concept of human microbiome validates the fact that human is a superorganism which presents as a complex entity of millions of lives surviving together as a single unit making it the holobiont humane. This is in lieu with the ancient philosophical concept of Holism postulated by Aristotle. Aristotle considered human body as a 'microcosm' or 'small universe'. With every new addition in the field of microbiome research; the contemporary science is coming at the verge of accepting this concept. All the microorganisms living inside or over human body are named as human microbiome. They play pivotal physiological roles in health states. Protection against pathogens, development of immune system, digestion and metabolism, synthesis of essential nutrients, detoxification and immune function regulation. The number and type of the microorganisms can be manipulated by some natural and engineering techniques. All these methods are collectively named as the microbiome modulation. The modulation is needed for changing the symptoms or the causes of various diseases to improve health status of the host. Major techniques of microbiome modulation so far in use incude, dietary modifications, fecel microbiota transplantation (FMT), antibiotics therapy, environment modification, microbiome engineering, phage therapy, microbial-specific drugs and prodrugs development. Wherever there is a scope of dietary interventions and environment modification; Tibbe Unani finds a scope there. It is due to the fact that these two factors are vastly discussed in Kulliyate Tibb under the head of Asbabe Failiyah. Therefore, it would be of great benefit to the humanity if the Unani scholars pay attention towards microbiome modulation in terms of designing, research and validation of a few novel methods.

Conclusion:

The contemporary medical world is looking forward to the promising role of microbiome modulation in improving healthcare. Unani scholars should also rejuvenate the ancient philosophical concept of Holism. Learning basic techniques of microbiome modulation and addition of novel methods after extensive research and validation should be emphasized. This will be beneficial for the more precise healthcare of the masses.

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