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CHANGES IN THE COMPOSITION OF THE BODY'S MICROBIOME IN VARIOUS PATHOLOGIES AND MODERN MEASURES TO ELIMINATE THEM

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Abstract. A variety of dynamic microbial communities that live in different body anatomical sites make up the human microbiome. As a result of the microbiome and host coevolution, these communities now significantly contribute to the promotion of human health. Therefore, alterations in the human microbiome have the potential to induce or worsen a number of illnesses. Since its discovery, several studies have emphasized the importance of microbiota in health and illness. Microbiota can be divided into four categories based on the localized areas: gastrointestinal, mouth, respiratory, and skin. Together with the host, the microbial populations maintain homeostasis and control immunological response. On the other hand, dysbiosis of the microbiota can result in diseases such as cancer, respiratory disorders, CVDs and dysregulation of body systems. We go over what is currently known about the relationship between microbiota and pathogenesis or host health in this review. The study on microbiota in healthy conditions, including immune regulation, colonization resistance, and the gut-brain axis, is first summarized. Next, we discuss the pathophysiology of microbiota dysbiosis in the onset and progression of disease, which is mainly linked to the generation of chronic inflammation, host immune response modulation, and dysregulation of community composition. Lastly, we present clinical strategies that use microbiota to treat diseases, including fecal microbial transplantation and microbiota regulation. Despite advancements in traditional prevention and treatment techniques, CVD remains a major worldwide health burden with lingering risks. A growing body of research indicates that the gut microbiota plays a crucial but little-studied role in cardiovascular health through intricate interactions between immunological, metabolic, and inflammatory processes. The formation and progression of atherosclerosis, hypertension, heart failure, and arrhythmias are all directly impacted by key microbial metabolites such TMAO, SCFAs, BAs, and LPS, which have been identified as significant modulators of endothelial function, lipid metabolism, and systemic inflammation.

Keywords. Blood, metabolite problems, cardiovascular diseases, microbes, erythrocytes, microbiome, nervous system

Introduction. Since developments made it possible to sequence entire species' genomes, we have amassed an exponential amount of data on genome sequencing from microorganisms. The number of full or nearly complete bacterial genomes that have been sequenced exceeds 130,000. At the same time, terabytes of sequencing data have been generated, and over 20,000 metagenomic projects are publically accessible. Our understanding of microbial systems has advanced to a genuinely revolutionary level thanks to this astounding development of knowledge about the genetic architecture of microorganisms. We can now efficiently create complex biological systems that carry out desired functions because we have a systems-level understanding of the interacting networks of biological molecules, including genes and proteins. Synthetic biology is a new interdisciplinary field of study that has emerged as a result of this technological achievement and the development of other important enabling techniques, such as

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gene synthesis [1,2,3,4]. However, in the natural world, microorganisms almost never exist alone; instead, they always form a microbial community, each of which occupies a specific niche. Furthermore, they live in a variety of biotic and abiotic settings. This collection of microorganisms, known as the microbiome, has long coexisted with the human body and evolved to play a significant role in its physiological processes, including immunological development, metabolism, and behavioral responses. Because microbial populations and the living host have such a complex interaction, it is not unexpected that when one is disrupted, the other is frequently disrupted as well. That is, a variety of the host's illness states, from metabolic to immunological and behavioral problems, can be linked to a disrupted microbiome, or dysbiosis. Recent years have seen a sharp rise in the study of the human microbiome and its connections to various illnesses [5,6,7,8]. Engineering microbiomes to change and reprogram the gut microbiome's composition and function as a novel treatment approach is gaining traction as the significance of the connection between human-associated microbial populations and disease development becomes clear. According to recent research, CVDs include heart failure (HF), atrial fibrillation, stroke, and coronary artery disease are linked to signs of IBD. Atherosclerosis/endothelial dysfunction, dyslipidemia, thrombocytosis, gut microbiota dysbiosis, and IBD medicines were among the mechanisms linking IBD to CVDs. According to reports, intestinal permeability is increased by gut dysbiosis in IBD, allowing bacterial products to enter the bloodstream. This leads to endothelial dysfunction and inflammation, both of which are factors in CVD. For example, the enrichment in *Streptococcus spp.- Enterobacteriaceae*, including *E. coli* and the changes in the *Firmicutes/Bacteroidetes* ratio linked to high blood pressure (BP) that are seen in individuals with IBD and CVD [9,10,11,12]. There are still significant questions, though. Despite the substantial correlations between gut microorganisms and CVD, it might be challenging to establish direct causation, as noted in a review.5. Mechanistic study is necessary to determine the bacterial taxa or pathways that lead to cardiac dysfunction or vascular inflammation and to comprehend how they interact with host genetics and food. Disparities in microbiome sequencing methods, differences in patient diets and medication schedules, and a lack of consistent measures are examples of methodological issues that make data interpretation more difficult. Importantly, clinical recommendations for determining the risk of CVD do not yet incorporate the microbiota. Large randomized trials examining whether changing the microbiota will enhance hard CV outcomes are similarly lacking [13,14,15,16]. This review examines the gut microbiota's composition and how it varies in CVDs, the mechanistic roles of metabolites derived from microbes in cardiovascular pathophysiology, and the connections between gut dysbiosis and inflammation, immunological responses, endothelial dysfunction, and cardiac fibroblast and cardiomyocyte dysfunction. Additionally, we go over therapies that target the gut-heart axis, such as probiotics, dietary changes, and new microbiota-based methods. By exploring these intricate relationships, we hope to provide a thorough grasp of how gut microbiota affects the pathophysiology of CVDs and identify possible avenues for the development of innovative precision medicine treatments [17,18,19,24].

The main purpose of this brief review is to analyze changes in the composition of the body's microbiome in various pathologies and modern measures to eliminate them based on reputable scientific papers.

Over the past few decades, research on the microbiome has grown quickly and is currently a highly popular issue among scientists and the general public. Environmental microbiome research served as the foundation for the field's historical development, which saw eukaryotes as inextricably linked to the microbial community they coexist with. After all,

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trillions of microscopic species dwell with the host in the ecosystem that is the human body. Therefore, the collection of genes from all microorganisms that live in nearly every region of the human body is referred to as the "microbiome" in science. Accordingly, the microbiome is regarded as a second genome that coexists with the host in a symbiotic relationship. Microbiome interactions are important for human health because of this relationship, which can be neutral, harmful, or good. With an estimated 50–100 times more genes, the diverse and complex microbiome functions as a functional extension of host genomes. By containing different kinds of enzymatic proteins, these additional genes help to regulate host physiology by regulating the metabolites that are produced and, consequently, host metabolism [7-12]. Over time, a holistic approach based on the holobiont theory has been used rather than examining the interaction between a single microorganism and its host. Determining the core microbiota is also essential because it makes it easier to distinguish between an intermittent or temporal microbiome that is influenced by particular environmental factors. While transient microbiota varies over time, core microbiota is the microbial population that is consistently linked to a particular host genotype or environment. By recognizing these variations, the methodology used in microbiome research for therapeutic purposes can be improved using a suitable experimental, methodological, and statistical design [14-21].

Composition and diversity of the gut microbiota. A collection of microorganisms that live in the digestive tract, including bacteria, fungus, and viruses, is known as the gut microbiota. The composition and function can be affected by a number of factors, including age, food, mode of birth, and genetics. The digestive tract starts to colonize as soon as the baby is born.6. Similar to the host DNA, the gut microbiome's diversity and composition are distinct. The metagenome, or gene content of these microbiomes, is also referred to as our alternative genome. Even though there are hundreds of species, just roughly 30 to 40 genera make about 99 percent of the microbiota. Sixty percent of the dry bulk of feces is made up of bacteria. The most prevalent bacterial phyla in the human gut are *Firmicutes, Bacteroidetes, Actinobacteria* and *Proteobacteria;* the most often observed species are *Bacteroides, Clostridium, Faecalibacterium, and Prevotella.* The gut microbiota of individuals who use probiotic supplements is less varied than that of those who ingest foods that include naturally fermented bacteria (probiotics) and prebiotic fibers. Compared to formula-fed individuals, breastfed individuals have been demonstrated to produce a more diversified microbiome; however, there is also research that suggests females may have a somewhat lower variety than males [25-30].

Elements Affecting the Human Microbiota. Depending on the best conditions for growth, microorganisms live in the habitat of their choice. They are present on the exterior, interior, and entrance locations of the human body. The skin, eyes, and even the exposed areas beneath the nails are examples of external locations that harbor bacteria. The urogenital system, gastrointestinal tract (oral cavity), respiratory tract (mouth and nose), and skin surface fissures are the entry points for germs. In the meantime, the lungs, gut, bladder, kidneys, and vagina are among the internal body regions that are home to bacteria. Microbes typically flourish in environments that are conducive to their growth. It is therefore anticipated that these microbes will possess adaptation mechanisms to adjust to human microbiome circumstances that are similar to their favored natural habitat. The variety and number of microorganisms at various bodily locations are influenced by environmental parameters such temperature, pH, oxygen concentration, pressure, osmolarity, and nutrient source [9-15]. Our body temperature, for example, is ideal for harboring a wide variety of microorganisms. Other elements, such the availability of nutrition sources like sebum, alter the pH of the skin and serve as a source of carbon, which promotes the growth of particular microbial species. Fascinatingly, the thick layer

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of mucus covering the intestinal epithelium offers attachment sites for bacterial adhesion in addition to acting as a carbon source for microorganisms. Both internal and external variables influence the human microbiota's variety and abundance. Since the physiology of habitat locations promotes the growth of certain bacteria, intrinsic factors include the type of body habitats, as previously discussed. Age, gender, ethnicity, and genetics are other inherent elements that influence the composition of the microbiome. After the microbe has acclimated to its surroundings, the human microbiome is usually resilient and robust. Overall, depending on the body's natural environment, the human microbiome flourishes under ideal growth conditions. Alterations to the body's natural environment cause the diversity and composition of microorganisms to change in order to adapt, which may lead to illness [17-22].

Gut Permeability and Heart Failure. The incapacity of the heart to pump enough blood to meet the body's needs is the hallmark of heart failure (HF), a complex clinical disease. Recent data indicates that HF is linked to changes in the makeup of the gut microbiota that favor pathogenic and pro-inflammatory species. According to the "gut hypothesis of heart failure," the gut microbiota's composition is disrupted and intestinal permeability is increased by HF-induced variables such as decreased intestinal perfusion and altered gut motility. These disorders erode the integrity of the intestinal barrier by further impairing tight junctions. In addition, intestinal edema brought on by venous congestion exacerbates the failure of the epithelial barrier. Oxidative stress, another hallmark of HF, damages epithelial cells and impairs the synthesis of protective mucins, thereby aggravating gut barrier breakdown. This leads to a compromised intestinal barrier, a selective interface between the host and gut microbiota, resulting in increased gut permeability. As mentioned before, the alteration in gut permeability leads to an increased passage of pathogens and toxins, such as LPS, from the gut into the systemic circulation. This state of “leaky gut” is associated with chronic systemic inflammation, characterized by elevated pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, which contribute to myocardial remodeling and cardiac dysfunction and can exacerbate HF symptoms and severity [23-28].

Transplanting Fecal Microbiota and New Approaches. The goal of fecal microbiota transplantation is to reestablish a diversified and balanced gut microbiome by introducing processed stool from a healthy donor into the patient's digestive system. The idea behind this strategy is that reinstalling good microbial populations can treat a number of disorders, particularly those related to gut dysbiosis. FMT's therapeutic impact is believed to result from: (i) replenishing depleted or absent beneficial bacteria; (ii) competing with harmful microorganisms (bacterial interference); (iii) resuming the production of important metabolites (e.g., secondary BAs, SCFAs); (iv) adjusting metabolic pathways and the immune system. In clinical settings, FMT has demonstrated some positive outcomes when used to treat diarrhea linked to Clostridium difficile (CD) [17-21]. The cardiovascular advantages of nonviable microbial products such SCFAs, enzymes, and peptides, as well as FMT and postbiotics, are being studied. Without the dangers of live organisms, they provide the benefits of stability and precise distribution. A natural and efficient strategy to avoid or lessen gut dysbiosis, which is a major contributing factor to CVDs, is to engage in regular physical activity. Exercise and dietary changes that target the gut microbiota may provide new therapeutic strategies for the prevention and treatment of CVD. Promising approaches to managing CVD include focusing on the gut-heart axis using probiotics, prebiotics, dietary changes, medications, and new techniques like FMT. These methods demonstrate how altering the gut microbiota can lower systemic inflammation, improve lipid profiles, and improve cardiovascular health in general [26-31].

Future Prospects and Difficulties. Despite significant advancements in our knowledge of gut microbiota, a number of questions still need to be addressed in order to fully unravel the gut-

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heart axis and translate findings into clinical practice. Advanced molecular and systems biology tools are required to understand how certain gut microbiota-derived metabolites, such as TMAO, SCFAs, and LPS, affect cardiovascular health, and integrating multiomics approaches, such as metabolomics, proteomics, and transcriptomics, can lead to a deeper understanding of these interactions. The gut-heart axis describes the intricate relationship between gut microbiota, their metabolites, and the risk and progression of cardiovascular disease. For instance, in both animal models and extensive human research, excessive TMAO levels—which arise from the microbial metabolism of dietary choline and carnitine—are highly linked to an increased risk of atherosclerosis and severe cardiac events [3-8]. On the other hand, SCFAs often improve vascular function and reduce inflammation to provide protective effects, while their effects can vary based on host characteristics and microbial makeup. Despite the fact that animal models are incredibly useful for studying the role of gut microbiota, it is still difficult to translate these findings to large-scale human research and clinical cohorts because of individual heterogeneity, nutrition, lifestyle, and drug usage. Understanding the interindividual variance in gut microbiota composition and how it interacts with host genetics is therefore also essential. To maximize gut microbiota for cardiovascular health, customized therapies such as dietary changes, prebiotics, probiotics, or postbiotics could be created. Novel treatment approaches, such microbiota transplantation or small compounds that target toxic metabolites, need investigation and clinical testing. Pharmacomicrobiomics' study of microbiota-drug interactions can improve medication efficacy and reduce adverse effects in CVD treatments. Both the risk of CVD and the metabolism of xenobiotics are significantly influenced by the gut microbiota, making it a crucial area for precision cardiology to create tailored strategies [11-15]. Indeed, there is growing recognition that the microbiota plays a minimally concentrated role in drug metabolism. Validating hypotheses requires the use of human trials and carefully planned experimental models. It is still very difficult to transform preclinical discoveries into safe, scalable, and effective interventions for a variety of groups. Fecal microbiota transplantation and microbiota-based treatments present ethical and legal issues that need for strict regulations and oversight systems. One area of cardiovascular treatment that shows promise is the gut bacteria. In order to improve cardiovascular outcomes and patient care, it will be possible to develop innovative preventive, diagnostic, and therapeutic treatments by addressing these future trends and difficulties [21-25].

Discussion. The gut microbiota plays a critical role in controlling cardiovascular health and illness, according to new research. Through metabolites, immunological regulation, and systemic signaling pathways, the gut microbiota—a complex population of microorganisms living in the gastrointestinal tract—interacts with its host and shapes cardiovascular physiology. An imbalance in the composition of gut microbes, known as dysbiosis, has been connected to a number of cardiovascular illnesses (CVDs), such as atherosclerosis, heart failure, and hypertension. Important microbial metabolites such lipopolysaccharides (LPS), trimethylamine N-oxide (TMAO), and short-chain fatty acids (SCFAs) have been linked to metabolic dysregulation, endothelial dysfunction, cardiac fibroblast dysfunction, cardiomyocyte dysfunction, and systemic inflammation [1,9,10,12]. The dynamic interaction between the gut and the heart is examined in this review, with particular attention paid to the following topics: the composition of the gut microbiota and its changes in cardiovascular disease; metabolites derived from microorganisms and their mechanistic roles in cardiovascular pathophysiology; the pathways that connect gut dysbiosis to inflammation, immunological responses, endothelial, cardiac fibroblast, and cardiomyocyte dysfunction; and potential therapeutic approaches that target the gut-heart axis, such as dietary changes, probiotics, probiotics, and emerging

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microbiota-based approaches. By revealing these complex connections, we hope to offer a thorough grasp of how gut microbiota influence CVD pathogenesis and talk about possible directions for cutting-edge precision medicine treatments. Generally speaking, changing the gut microbial makeup or its metabolomic function can be used to modulate the microbiome's function, often known as "microbiome engineering." According to reports, these changes are mostly caused by giving a particular microbe (or group of microorganisms), prebiotics, or bioactive metabolites to induce a change in the microbiome's composition and functions in order to restore the disturbed metabolic function. Furthermore, a more logical and accurate therapeutic action can be offered by synthetic consortia of microorganisms or created probiotics [2,11,13,14[. Numerous genetic tools have been discovered and developed since the early days of designing probiotics for such interventions in order to carry out therapeutic actions in a more complicated and precise manner. Giving a thorough grasp of developments in the microbiome–host connection for human health is the aim of this review. In order to facilitate thorough microbiome research and reliable microbiome engineering, this Review also attempts to present a nonexhaustive list of studies that address the manipulation of the human microbiome to prevent or treat human disease, with a particular emphasis on multiomics approaches and the cellular reprogramming of microbes. With an emphasis on the microbiomes present in the skin, digestive, respiratory, urinary, and reproductive systems, we provide our current understanding of the connection between human health and disease development in this Review. Additionally, we go over a number of methods for modifying the human microbiome's makeup and function in order to treat the host. Lastly, we look at technologies that have the potential to significantly expand microbiome research and engineering, such as cellular reprogramming of microorganisms and multiomics techniques [20-24]. The combination of multi-omics techniques, biomarker validation, and artificial intelligence should be given top priority in future directions in order to unravel the gut-heart axis and make precision-based treatment approaches possible. Thorough longitudinal research, standardized techniques, and a variety of population studies are necessary to translate microbiome science into therapeutic practice. In the end, knowledge of and control over the gut microbiota presents a viable avenue to supplement conventional CVD treatment, maybe resulting in novel and individualized therapeutic and preventive measures [11,17,23,24].

Conclusion. One potential new target for the prevention and treatment of CVD is the alteration of the gut microbiota. Validating microbial biomarkers and optimizing microbiome-based therapies will require large-scale, standardized randomized studies with objective cardiovascular outcomes and comprehensive multi-omics analysis.

In order to decipher the gut-heart axis and facilitate precision-based treatment approaches, future initiatives should place a high priority on the integration of multi-omics techniques, biomarker validation, and artificial intelligence. Standardized procedures, broad demographic research, and thorough longitudinal investigations are necessary to translate microbiome science into therapeutic practice. Finally, a promising avenue to supplement conventional CVD care is the study and manipulation of the gut microbiota, which may result in novel and individualized therapeutic and preventive measures.

It is crucial to validate theories through human trials and carefully crafted experimental models. The translation of preclinical discoveries into safe, scalable, and effective interventions for a variety of groups is still a major challenge. Strong guidelines and monitoring mechanisms are necessary because microbiota-based therapeutics and fecal microbiota transplantation present ethical and regulatory issues. A promising area of cardiovascular treatment is the gut bacteria. The development of innovative preventive, diagnostic, and therapeutic approaches will be made

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possible by addressing these future directions and difficulties, which will eventually improve patient care and cardiovascular outcomes.

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