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Microbiota and Hypertension: Exploring the Gut-Heart Connection- A Review

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ABSTRACT:
Research on the microbiota-gut-heart axis and microbiota-gut-hypertension axis reveals the intricate relationship between gut microbiota and cardiovascular health. This review explores these connections, emphasizing the impact of gut microbiota on cardiovascular disease (CVD) and hypertension.The gut microbiota plays a crucial role in cardiovascular health through various mechanisms. One key mechanism is inflammation. Increased production of pro-inflammatory chemicals may be the outcome of dysbiosis, a variation in the diversity of the gut microbiota.These molecules can enter the bloodstream and contribute to systemic inflammation, which is a key driver of CVD and hypertension. It might be able to lessen inflammation and lower the chance of developing certain illnesses by adjusting the gut microbiota.Metabolism is another important aspect of the microbiota-gut-heart axis and microbiota-gut-hypertension axis. The conversion of food ingredients like fiber and polyphenols into bioactive molecules is aided by the gut flora. These compounds can have beneficial effects on cardiovascular health by reducing cholesterol levels, improving insulin sensitivity, and modulating blood pressure. Furthermore, the production of short-chain fatty acids (SCFAs), which have been connected to decreased inflammation and enhanced cardiovascular function, can be influenced by the gut microbiota.Therapeutic strategies targeting the gut microbiota show promise in improving cardiovascular outcomes. Probiotics, prebiotics, and dietary interventions can help restore a healthy gut microbiota composition. For example, probiotics containing beneficial bacteria like Lactobacillus and Bifidobacterium have been shown to reduce cholesterol levels and improve blood pressure. Prebiotics are indigestible food ingredients that encourage the formation of good bacteria. They may also be useful for heart health. Further research is needed to fully understand the mechanisms involved and to develop effective strategies for improving cardiovascular outcomes through gut microbiota modulation.

KEYWORDS: hypertension, cardio vascular disease,Trimethylamine, Short-chain fatty acids, spontaneously hypertensive rats, Wistar Kyoto controls, Antigen-presenting cells, Gut Microbiota, lipopolysaccharide, Intestinal fatty acid binding protein, T helper 17 cells, fecal microbiota transplantation.

I. INTRODUCTION:

The microorganisms that reside in the digestive systems of animals include bacteria, viruses, fungi, and archaea. These organisms are referred to as gut microbiota, gut microbiome, or gut flora.[1,2]., The human microbiome is mostly found in the gut. [3], The collective of all the gut microbiota's genomes is known as the gastrointestinal metagenome. [4].The microbiota present in the gut is highly varied, consisting of billions of microbes, but primarily dominated by four phyla: Firmicutes, Bacteroidetes, actinobacteria, and proteobacteria. Maintaining intestinal immunity and whole-body homeostasis depends on a delicate equilibrium in the compositionof the gut microbiota; any perturbation of this balance could have disastrous pathophysiological effects.One frequent term for an imbalance in gut microbiota is dysbiosis.[5].High blood pressure (HTN) is a major contributor to heart disease and stroke, as well as the primary risk factor for the morbidity and mortality associated with cardiovascular disease.[6] Each year, an

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estimated 9.4 million deaths worldwide are attributed to HTN. Despite this, the underlying causes of more than 90% of hypertension cases remain unknown according to physiological principles. [7-9]. Peripheral vascular disease, cardiac events, chronic renal disease, and hypertension are all significantly exacerbated by hypertension.[10].and various acute and chronic heart-related conditions, like obesity or metabolic syndrome, have been associated with insufficient or disrupted acquisition of the microbiome after birth or exposure to environmental microorganisms in early childhood. [11-16].Many studies have explored the link between blood pressure and the oral and gut microbiomes in both humans and animals. These studies indicate that the gut microbiota, along with genetic, environmental, age, and lifestyle factors, has a notable influence on HTN. Increasing evidence suggests that diet and gut microbiota are important environmental factors in regulating blood pressure.[17-20]. A specific metabolite called trimethylamine (TMA) is created when the bacteria in your gut break down choline, a nutrient present in red meat, eggs, poultry, and fish. This metabolite is then converted to trimethylamine N-oxide (TMAO) in your liver. [21,22]TMAO is associated with an unhealthy balance of gut bacteria, and researchers are investigating its potential link to the buildup of plaque in arteries and an elevated risk of cardiovascular events such as heart attacks and strokes. [23]

HUMAN: A Harbor for microbiota:

FIGURE.I.A HARBOR FOR MICROBIOTA

Humans harbor a diverse array of microorganisms throughout their bodies, including bacteria, archaea, viruses, and unicellular eukaryotes. This collection of microbes, known as the microbiota, colonizes various surfaces of the body exposed to the external environment such as the skin, genitourinary tract, gastrointestinal tract, respiratory tract.[24].The composition of the gut microbiota changes along the digestive tract. Typically, the stomach and small intestine host fewer bacterial species compared to the large intestine. [25,26].The human gut microbiota is mainly composed of two types of bacteria: Bacteroidetes and firmicutes. [27]. Other types, such as proteobacteria, Verrucomicrobiota, actinobacteria, fusobacteria, and cyanobacteria, are present but in smaller amounts.[28,29].

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FIGURE.II. THE MOST ABUNDANT BACTERIAL PHYLA AND GENERA FOUND IN THE MICROBIOTA OF THE HUMAN GUT.

THE MOST ABUNDANT BACTERIAL PHYLA AND GENERA FOUND IN THE MICROBIOTA OF THE HUMAN GUT

Phyla	Representative genera
• Firmicutes (60-80%)	• Ruminococcus • clostridium • lactobacillus • entereococcus
• Bacteroidetes (20-30%)	• Bacteroides • prevotella • xylanibacter
• Actinobacteria (<10%)	• Bifidobacterium
• Proteobacteria (<1%)	• Escherichia • enterobacterenterobacteriaceae

The human digestive system hosts a vast number of microorganisms, estimated to range from 10^13 to 10^14, [30]. which is similar to the estimated number of human body cells. Among these microorganisms, bacteria are the most abundant, with approximately 500-1000 different species in the gut. [31,32]. The main bacterial phyla, Bacteroidetes and Firmicutes, account for over 90% of the gut microbiota.[29]. The intestinal lining is shielded from the gut contents by a thick, intricate mucus layer. The types of microorganisms in the gut contents differ significantly from those in the mucus layer and those near the intestinal lining. Microbial colonization of the human gut begins shortly after birth, as infants are exposed to various microbes during birth. Infants born via cesarean section have different microbial compositions compared to those born vaginally. [33,34,66,67]. The composition of the intestinal microbiota varies throughout the mammalian gut, with varying concentrations of bacterial cells.[35-39]

THE SIGNIFICANCE OF THE FIRMICUTES/BACTEROIDETES RATIO IN HEALTH AND DISEASE:

Growing research indicates that changes in the Firmicutes (F) and Bacteroidetes (B) microbial communities, known as the F/B ratio, could serve as a valuable biomarker for various health conditions. This ratio typically increases from infancy to adulthood and continues to evolve with age. It appears to be particularly useful in distinguishing between different life stages, such as infants, adults, and the elderly, reflecting broader shifts in bacterial profiles.

Notably, a diet high in fat has been linked to a significant increase in the Firmicutes:Bacteroidetes (F:B) ratio, which is widely recognized as a marker of gut dysbiosis.

This study presents initial evidence linking hypertension (HTN) to altered gut microbiota, using two rat models of HTN and a small group of hypertensive patients. Key findings include:

- Reduced microbial diversity and significant increases in the F/B ratio in the hypertensive rat models, indicating gut dysbiosis in HTN.

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- This dysbiosis was associated with decreases in bacteria producing acetate and butyrate, and an increase in bacteria producing lactate.
- Gut microbiota dysbiosis was also observed in a small group of human hypertensive patients, suggesting clinical relevance.
- Oral minocycline restored balance to gut microbiota in a rat model of hypertension.

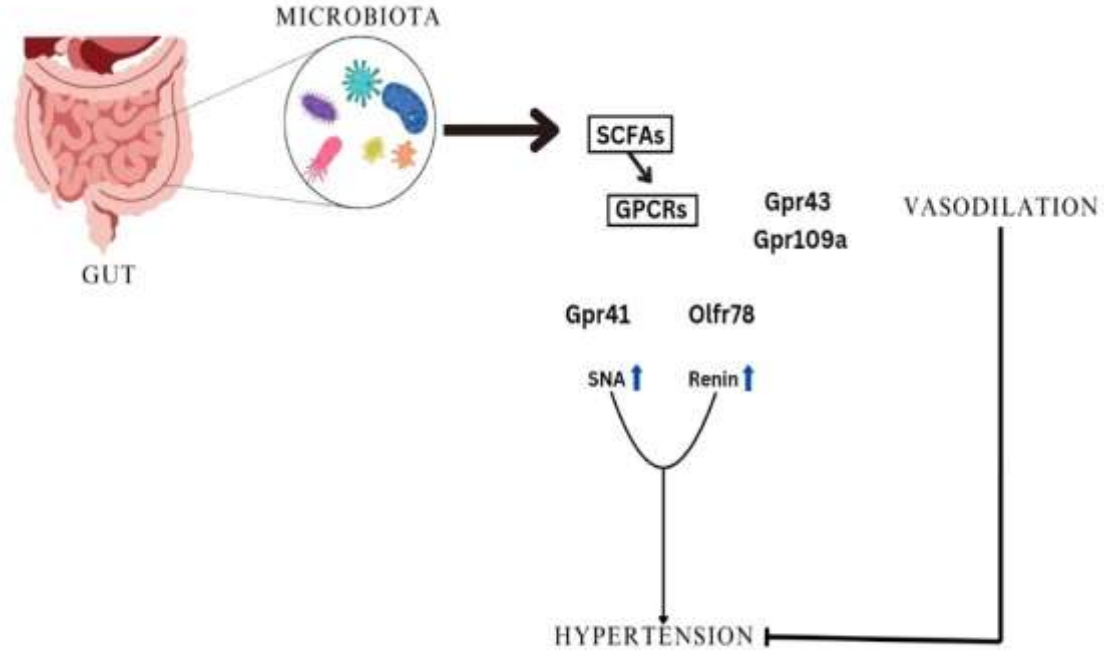
These results strongly suggest that gut microbiota play a role in the development of HTN in both animals and humans.[40-44].

GUT MICROBIOTA IMBALANCE AND HYPERTENSION: IMPLICATIONS OF BACTERIAL SHIFTS:

In animal models of hypertension, there was an observed rise in lactate-producing bacteria, which is noteworthy due to the association between elevated plasma lactate levels and increased blood pressure. Additionally, reductions in bacteria responsible for producing butyrate and acetate were observed in these models. Certain butyrate-producing bacteria can use acetate as an energy source to produce butyrate. This shift in bacterial composition suggests a potential link between gut microbiota dysbiosis and blood pressure alterations. Notably, the genus victivallis, a natural component of the human gut microbiota, plays a crucial role in the gut ecosystem and interacts with other microbes.[45-48].

MECHANISM OF DIETARY FIBER IMPACT ON BLOOD PRESSURE THROUGH GUT MICROBIOTA:

FIGURE.III.MECHANISM OF DIETARY FIBER IMPACT ON BLOOD PRESSURE THROUGH GUT MICROBIOTA



This flowchart illustrates how dietary fiber intake leads to the production of short-chain fatty acids by the gut microbiota.[49,50]. These SCFAs (Short-chain fatty acids) can then enter the host's bloodstream and activate GPCRs (G-protein coupled receptors), such as Gpr41 and Olfr78, leading to increased sympathetic nerve activity and renin secretion, ultimately resulting in elevated blood pressure. However, other GPCRs, such as Gpr43 and Gpr109a, can promote vasodilation, counteracting the effects of Gpr41 and Olfr78. [51-53].

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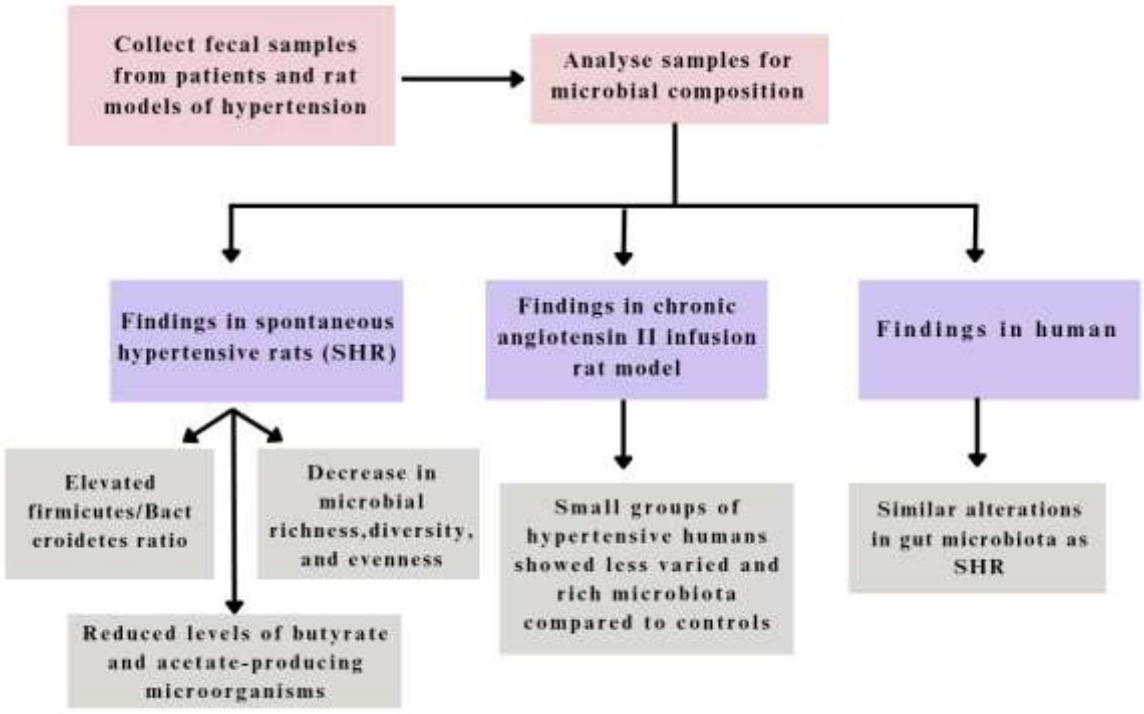
DYSBIOSIS OF GUT MICROBIOTA LINKED TO HYPERTENSION:

FIGURE.IV.DYSBIOSIS OF GUT MICROBIOTA LINKED TO HYPERTENSION



Gut dysbiosis has been observed in both animal models and patients with hypertension (HTN). For instance, spontaneously hypertensive rats (SHRs) showed gut-related pathophysiological changes.[54]., including decreased goblet cell numbers, shortened villi length, and increased fibrosis, compared to age-matched normotensive Wistar Kyoto (WKY) controls. These changes were more prominent in adult SHRs than in juvenile SHRs that had not yet developed hypertension. Interestingly, prehypertensive juvenile SHRs exhibited reduced levels of several tight junction proteins but had similar gut permeability compared to juvenile WKY rats. These findings suggest that gut abnormalities occur before the onset of high blood pressure in SHRs. Further evidence supporting the idea that gut dysbiosis plays a causative role in HTN comes from fecal microbiota transplantation (FMT) experiments. In these experiments, transferring dysbiotic fecal samples from hypertensive patients to germ-free mice or feces from hypertensive stroke-prone rats to FMT resulted in an increase in blood pressure, indicating the need for further investigation to determine the potential mechanisms underlying the FMT-induced rise in blood pressure.[20,55-56].

IMPACT OF HIGH SALT CONSUMPTION ON GUT MICROBIOTA AND BLOOD PRESSURE:

High salt consumption has been demonstrated to alter the composition of the gut microbiota (GM) in both human and mouse models. This alteration results in an increase in Firmicutes, Proteobacteria, and the Prevotella genus of bacteria, all of which have been associated with elevated blood pressure (BP). Specifically, high salt intake reduces the presence of Lactobacillus murinus (L. murinus). Treatment with L. murinus has been shown to prevent salt-induced exacerbation of experimental autoimmune encephalomyelitis and salt-sensitive hypertension by modulating Th17 cells. In humans, a moderate increase in dietary salt reduces the survival of Lactobacillus species, leading to an increase in T helper 17 cells and higher BP. [57].

Additionally, excessive dietary salt has been linked to changes in the GM, inflammation,

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and hypertension. High salt intake is associated with increased formation of costimulatory ligands and IsoLG protein adducts in antigen-presenting cells (APCs), resulting in heightened intestinal and vascular inflammation and hypertension. [58].

Furthermore, high salt intake is correlated with enhanced gut-targeting proinflammatory Th17 cells, lipopolysaccharide (LPS), and intestinal fatty acid binding protein (l-FABP) plasma levels. These factors significantly contribute to enhanced intestinal permeability and inflammation in patients with high blood pressure. The significant elevation of zonulin, a modulator of gut epithelium tight junction protein, supports the breakdown of the gut barrier in individuals with high blood pressure. [59-60].

THERAPEUTIC IMPLICATIONS: MODULATING MICROBIOTA FOR BLOOD PRESSURE CONTROL:

The gut microbiota plays an essential role in human health. Researchers are exploring novel methods to manage metabolic diseases, including hypertension and cardiovascular disorders, by studying the gut microbiota. This research may lead to innovative treatments for these conditions.[61,62].

GUT MICROBIOTA AND HYPERTENSION:

The gut microbiota has emerged as a key player in the development and progression of hypertension. Targeting the gut microbiota could open up new avenues for hypertension treatment. The gut microbiota interacts with various host systems and organs involved in blood pressure regulation, such as the immune system, gut, and spleen.

Research on the role of the gut microbiota in treatment-resistant hypertension (rHTN) is ongoing, although progress has been limited by a lack of suitable animal models.

ANTIBIOTICS AND BLOOD PRESSURE MEDICATION:

Alterations in the abundance of gut bacteria, which can occur due to the use of broad-spectrum antibiotics, can affect the host's digestive health and function. [63]. There is also interest in how the gut microbiota may affect the metabolism of antihypertensive medications, potentially leading to treatment resistance. In one study, hypertensive rats treated with antibiotics to reduce their gut microbiota responded better to the angiotensin-converting enzyme inhibitor captopril, suggesting a link between the gut microbiota and drug effectiveness. [61].

NITRIC OXIDE PRODUCTION:

The oral microbiota plays a role in regulating blood pressure by producing nitric oxide. Nitric oxide has vasodilatory effects, which can help reduce blood pressure. [64,65]

FUTURE RESEARCH:

Future research should focus on elucidating the mechanisms by which the gut microbiota contributes to resistant hypertension and exploring its enzymatic activities and their impact on drug metabolism. [61].

II. CONCLUSION:

In summary, understanding the microbiota-gut-heart axis and the microbiota-gut-hypertension axis is crucial for developing targeted interventions to improve cardiovascular health. Further research is necessary to uncover the specific mechanisms involved and translate these findings into clinical applications. The gut microbiota shows promise as a potential therapeutic target for managing cardiovascular diseases, providing new avenues for treatment.

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