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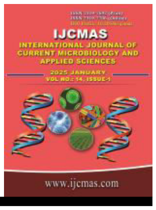

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Modulating Gut Fermentation: A Novel Approach to Managing Hypertension and Modulation of Gut Fermentation

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The cardiovascular disease is mounting a serious scientific and public concern, as it is responsible for 30% (17.3 million) of deaths annually, foremost among non-communicable diseases. For those living with the disease, quality of life is impacted by a significant number of having an associated disability. Presently, the treatment of hypertension is accompanied by the application of agents that act on the angiotensin system. This type of treatment has its implications, as exclusively reported by the various workers. However, the main concern of this review is to draw a different line of a treatment plan that should be based on remediation for causal agents of hypertension rather than working on the artificial reduction of blood osmotic potential. It is observed from the review of available literature that the modulation of gut flora and reducing the duration of fermentation in the gut could be effective in the reduction of hypertension. So far, it has now been successfully established that gut fermentation, especially protein fermentation, extensively affects the homeostasis of the gut-liver axis, allowing thereby the entry of unwanted compounds into the liver, which in a later course, blood too. Therefore, modulation of gut microbiota could help rectify the problem of leaky gut.

Introduction

The prevalence of diabetes and hypertension has emerged as significant health threats within Indian society, influenced by the shift from traditional Ayurvedic practices to allopathic treatments, a transformation catalyzed by British colonization. The widespread adoption of allopathic medicine has resulted in alternative treatments being categorized under a generalized term, "alternative medicine." This rapid proliferation of allopathy can primarily be attributed to its efficacy in ensuring speedy recovery; however, the associated side effects cannot be overlooked. While the societal endorsement of this transition remains contentious, it is imperative to recognize that the manifestation of diseases is inherently linked to environmental factors. Consequently, it raises the question of how a uniform occurrence of a specific disorder can be observed globally. This article aims to critically examine the various etiological factors contributing to hypertension, focusing on the determinants of blood hydrodynamics and evaluating the current therapeutic methodologies. The review will address the following key issues:

1. Products of autointoxication in large bowel
a. Intestinal microflora
b. Fermentation Products in Gut
2. Gut toxins and its impact on liver health
3. Transportability of petrification products to Blood
4. Compounds so formed and their impact on blood hydrodynamics.
5. Suspected mechanism

Products of autointoxication in the large bowel

Since the late 17th century, research on gut intoxication has been ongoing. Unfortunately, it did not receive significant attention within the scientific community until the advent of probiotics. French physician Charles Bouchard proposed the theory of 'autointoxication,' which posited that 'man is inhabited by lower organisms,' primarily in the distal part of the gastrointestinal tract (GIT) (Bouchard, 1917). He suggested that these organisms could cause internal 'poisoning' and subsequent disease if not eliminated. However, this theory did not substantially stimulate research on the role of intestinal microbes in health.

Fast forward to the present, the significance of the human microbiome has emerged as a crucial moderator in the interactions between food and the human body. This shift in perspective has propelled research in this area from a marginalized position to one of optimism, with great potential and numerous possibilities (Manon, 2018). There is a growing body of evidence indicating that dysbiosis of the gut microbiota is associated with the pathogenesis of both intestinal and extra-intestinal disorders. Extra-intestinal disorders linked to gut microbiota dysbiosis include allergies, asthma, metabolic syndrome, cardiovascular disease, and obesity (Simon *et al.,* 2015).

Intestinal Microflora

The colonic microbiota plays a crucial role in human digestive physiology and significantly contributes to homeostasis in the large bowel. The microbiome likely encompasses the largest number of different bacterial species compared to any other body part (Quigley, 2013). The colon contains a densely populated microbial ecosystem with up to 10^{12} cells/g of intestinal content (Guarner and Malagelada, 2003). These bacteria represent between 300 and 1000 different species. Research suggests that the relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather a mutualistic, symbiotic relationship (Cynthia, 2005). However, under certain conditions, some species are capable of causing disease by initiating infection or increasing cancer risk for the host (Sherwood *et al.,* 2013; James *et al.,* 2018).

The adult human distal gut microbial community is typically dominated by two bacterial phyla: Firmicutes and Bacteroidetes (Michael *et al.,* 2009). Some commonly occurring species include *Achromobacter* spp., *Acidaminococcus fermentans*, *Acinetobacter calcoaceticus, Actinomyces* spp., *Aeromonas* spp., *Alcaligenes faecalis*, *Bacillus* spp., *Bifidobacterium* spp., *Butyrivibrio fibrosolvens*, *Campylobacter* spp., *Clostridium* difficile, *Mycobacteria* spp., *Mycoplasma* spp., *Pseudomonas aeruginosa*, *Ruminococcus bromii*, *Sarcina* spp., *Staphylococcus aureus*, and *Yersinia enterocolitica* (Todar, 2012).

The principal metabolic activities of colonic microorganisms are associated with carbohydrate and protein digestion. Nutrients of dietary and host origin support the growth of intestinal organisms. Short-chain fatty acids (SCFAs), predominantly acetate, propionate, and butyrate, are the principal metabolites generated during the catabolism of carbohydrates and proteins. In contrast, protein digestion yields a greater diversity of end products, including SCFAs, amines, phenols, indoles, thiols, CO_2, H_2, and H_2S, many of which possess toxic properties (Macfarlane and Macfarlane, 2012). The majority of SCFAs are absorbed from the gut and metabolized in various body tissues, contributing significantly to the body's daily energy requirements.

The gut microbiota is involved in the regulation of multiple host metabolic pathways, resulting in interactive host-microbiota metabolic, signalling, and immune-inflammatory axes that physiologically connect the gut, liver, muscle, and brain (Jeremy *et al.,* 2012; Bäckhed *et al.,* 2005; Filippo *et al.,* 2010; Laparra and Sanz, 2010).

Fermentation Products in Gut

The human gut can be considered as a bioreactor where fermentation occurs under ambient conditions. The resultant compounds formed during this process depend on various factors, primarily the ingested foodstuffs. It is generally accepted that carbohydrate fermentation results in beneficial effects for the host due to the generation of short-chain fatty acids (SCFAs), along with rhamnose, fucose, arabinose, xylose, mannose, galactose, glucose, and uronic acid (Wong *et al.,* 2012), as well as branched-chain volatile fatty acids (VFA) such as isobutyrate, valerate, and isovalerate, which are formed by the metabolism of branched-chain amino acids like valine, leucine, and isoleucine (Macfarlane *et al.,* 1992). In contrast, protein fermentation is considered detrimental to host health. Protein fermentation primarily occurs in the distal colon when carbohydrates are depleted, resulting in the production of potentially toxic metabolites such as ammonia, amines, phenols, and sulfides (Windey *et al.,* 2012; Macfarlane and Macfarlane, 2011).

Proteins and trichloroacetic acid-soluble peptides are present in high concentrations in human intestinal contents and feces. Free amino acids are also detected in millimolar amounts in colon contents, with hydroxyproline, alanine, lysine, and valine predominating, indicating that a wide variety of organic nitrogen-containing compounds are available for fermentation by intestinal bacteria (Macfarlane and Macfarlane, 1997). Protein breakdown and dissimilatory amino acid metabolism result in the formation of several putatively toxic metabolites, including phenols, indoles, amines (Henderickx, and Decuypere, 1973), and amides (Smith and Macfarlane, 1998). The formation of phenol, p-cresol, phenylpropionate, phenylacetate, and phenylpropionate are the principal phenolic compounds formed from all three substrates, along with hydroxyphenylpropionate and indole. However, p-cresol, phenylacetate, phenylpropionate, 4-ethylphenol, indole, indoleacetic, and indolepropionate are not metabolized by colonic bacteria. Hydroxy-phenylacetate and hydroxyphenylpropionate are hydrolyzed to p-cresol and phenylpropionate, respectively. Indolepyruvate is either converted to indole acetate or metabolized into indole. Indolepropionate, and to a lesser degree, indoleacetate, are produced from indolelactate (Duynhoven *et al.,* 2011).

Fate of Fermentation Products

The gut microbiota is integral to regulating multiple host metabolic pathways, giving rise to interactive host-microbiota metabolic, signaling, and immune-inflammatory axes that physiologically connect the gut, liver, muscle, and brain (Macfarlane and Macfarlane, 2012). Dietary polyphenols in their intact forms have limited bioavailability, with low circulating levels in plasma. A significant portion of these polyphenols persists in the colon, where resident microbiota produces metabolites that can undergo further metabolism upon entering systemic circulation (Saura-Calixto *et al.,* 2007). Polyphenol intestinal bio-accessibility was estimated using an in vitro gastrointestinal model, wherein food polyphenols are released by enzyme digestion and colonic fermentation. The mean daily intake of polyphenols in the Spanish diet was estimated to be between 2590-3016 mg/person/day. The amount of non-extractable polyphenols was nearly double that of extractable polyphenols. Approximately 48% of dietary polyphenols are bio-accessible in the small intestine, while 42% become bio-accessible in the large intestine (Hoover, 1978). The hindgut is a major site for sodium absorption and also absorbs significant quantities of water and variable percentages of potassium, calcium, phosphorus, cobalt, manganese, magnesium, copper, and zinc.

Ammonia absorption from the hindgut has been shown to contribute 39% of the total non-protein nitrogen absorbed into body fluids (McDonald, 1948). Along with ammonia (Boodeker *et al.,* 1990; Dumas *et al.,* 2006), amines are also absorbed in smaller quantities (Henderickx and Decuypere, 1973), serving as nitrogen sources for synthesizing non-essential amino acids and other compounds in the gut wall and liver. Ammonia net absorption was drastically reduced when volatile fatty acids were omitted from the buffer solutions and replaced by lactic acid (Noverr *et al.,* 2004).

The hindgut sustains a microbial population actively engaged in the conversion of hygroscopic or osmotically active materials into absorbable molecules. In herbivores and omnivores, the passage of more slowly digested dietary constituents through the small intestine encourages the movement of large amounts of water into the hindgut (Ridlon *et al.,* 2006). This water contains appreciable quantities of organic compounds and minerals. The metabolism of organic materials assists in the absorption of water, sodium, and other essential minerals, providing the host animal with an additional supply of energy in the form of volatile fatty acids (Alverdy and Chang, 2008).

Recent research has established the role of gut microbiota in nonalcoholic steatohepatitis (de Faria *et al.,* 2018), allergies (Carding *et al.,* 2015), gallstone formation (Ramírez-Pérez, *et al.,* 2017), and inflammatory bowel disease (Frank *et al.,* 2007; Schilderink *et al.,* 2013). The composition of gut microbiomes is highly flexible and significantly affected by dietary alterations (Turnbaugh *et al.,* 2008), and the application of antibiotics (Turnbaugh *et al.,* 2006; Jernberg *et al.,* 2007). Consequently, it is concluded that human metabolism is an amalgamation of microbial and human attributes (Lawrence *et al.,* 2014). The gene encoding salt hydrolase is enriched in gut microbiomes, and enteric bacteria carry out a wide range of bile acid modifications (Steven *et al.,* 2006; Ridlon *et al.,* 2006), naturally affecting the microbial composition.

Gut toxins and their impact on liver health

Due to its anatomical position and unique vascular system, the liver is particularly susceptible to exposure to microbial products from the gut. Despite the large microbial population in the gut, translocation of microbes or microbial products into the liver and systemic circulation is prevented by the gut epithelial barrier function and the liver's cleansing and detoxifying capabilities in healthy individuals.

The term “Gut-Liver Axis” (GLA) was first used by Volta *et al.,* (1987) to describe the production of IgA antibodies directed against intestinal microorganisms and food antigens in liver cirrhosis. However, the GLA now encompasses gut microbiota, intestinal barrier function, mucosal innate immune response, antigen trafficking, liver insult, and hepatic and gut metabolic disorders.

The gut microbiota consists of trillions of commensal microorganisms residing in the human gut, which are essential for preserving the integrity of the mucosal barrier function. It is vital for the maturation of gut-associated lymphoid tissue (GALT), the secretion of IgA, and the production of antimicrobial peptides. Specific disease dysbiotic patterns have been recognized through improved analytical intestinal microbiology methodologies, with a focus on conditions such as leaky gut (Ilan, 2012).

Trafficking across the intestinal mucosa occurs under the tight control of tight junctions (TJs), dynamic structures that play crucial roles in both physiological and pathological conditions. The discovery of zonulin, a molecule that reversibly modulates TJ permeability within tolerance limits, has elucidated how intestinal permeability contributes to health and disease (Fasano, 2011). The control of trafficking is modulated within the ranges of immunotolerance (Szabo *et al.,* 2007).

Innate immune cells, particularly dendritic cells (DCs), play a key role in sensing and regulating pathogenesis, further engaging adaptive immune responses for pathogen elimination. Pattern recognition receptors (PRRs) are responsible for sensing harmful bacteria and their products in the intestinal lumen, prompting GALT (including Peyer's patches, lamina propria lymphocytes, intraepithelial lymphocytes, and mesenteric lymph nodes) to initiate immune responses.

Research has shown that the recent increase in the consumption of refined carbohydrates conditions the microbiota, leading to an obesogenic westernized microbiome and increased intestinal translocation of bacterial endotoxins. A study indicated that a moderate reduction in fructose and sugar intake could improve BMI in overweight and/or obese children (Vajro *et al.,* 2013).

Gut microbiota produces enzymes capable of catalyzing the conversion of dietary choline to dimethylamine and trimethylamine (TMA), which are subsequently cleared by the liver. This microbial conversion reduces choline bioavailability, leading to fatty acid influx into the liver and the generation of reactive oxidative species through fatty acid reprocessing and oxidative stress (Dumas *et al.,* 2006). Elevated levels of trimethylamine-N-oxide are also associated with cardiovascular disease.

Bile acids, known for their bacteriostatic activity, play a vital role in the critical control of bacterial flora within the gut-liver axis, feedback regulation of lipids, and glucose homeostasis. The nuclear bile acid receptor FXR, strongly expressed in the liver and intestine, regulates these processes, reducing circulating bile acids via a feedback mechanism (Fuchs, 2012).

Energy and glucose homeostasis are regulated by food intake and liver glucose production. Wang *et al.,* (2008) reported that lipids in the upper intestine might activate an intestine-brain-liver neural axis to inhibit glucose production. The endocannabinoid (eCB) system, a group of endogenous cannabinoid receptors located throughout the central and peripheral nervous systems, plays critical roles in energy balance, intestinal permeability, and immunity. The eCB system controls obesity and its inflammatory complications through direct and indirect actions. The gut microbiota modulates the intestinal eCB system tone, which in turn regulates gut permeability and plasma lipopolysaccharide levels. Thus, the gut microbiota may influence adipose tissue physiology through LPS-eCB system regulatory loops and play critical roles in adipose tissue plasticity during obesity (Cluny *et al.,* 2012).

This disease spectrum includes simple steatosis to non-alcoholic steatohepatitis (NASH), histologically characterized by hepatocyte injury, inflammation, and varying degrees of fibrosis, eventually progressing to cirrhosis in some patients.

Impact of Gut Intoxicants on Plasma Biochemistry

A vast amount of literature is available to explain the role of gut microflora in human metabolism (Santacruz *et al.,* 2010). A broad, drug-like phase II metabolic response of the host to metabolites generated by the microbiome has been observed, suggesting that the gut microflora directly impacts the host's drug metabolism capacity (William *et al.,* 2009). This capacity is severely affected by the ingestion of dietary protein (Takashi *et al.,* 2014; Xie *et al.,* 2013). There exists a checkpoint within the gut-liver axis (GLA) that filters unwanted materials from entering the hepatic portal system. Microflora plays a vital role in maintaining this gut-liver axis.

Disturbances in the homeostasis between bacteria and host-derived signals at the epithelial level can lead to a breakdown in intestinal barrier function, fostering "bacterial translocation." Bacterial translocation refers to the migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes or other extra-intestinal organs and sites (Comparea *et al.,* 2012). Over the past decade, significant contributions of the gut microbiota in regulating and impairing energy homeostasis have been recognized, leading to metabolic disorders such as metabolic endotoxemia and type 2 diabetes mellitus (NIDDM-2). This is evidenced by numerous inflammatory biomarkers associated with obesity, diabetes, and other adverse outcomes (Nagpal *et al.,* 2015).

A substantial number of chemical species found in systemic circulation arise due to the presence of microbiomes. On average, 10% of detectable endogenous circulatory serum metabolites vary in concentration by at least 50% between two mouse livers. Several microbiome-affected molecules identified in the serum of carnivores are either potentially harmful (uremic toxins) or beneficial to the host. A broad drug-like phase II metabolic response of host species generated by microbiomes is evidenced by the exclusive presence of numerous sulfate, glycine-conjugated, and glucuronide adducts in serum (Ridlon *et al.,* 2006).

Compounds reported in the gut include indole derivatives (tryptophan, N-acetyl tryptophan, indoxyl sulfate, serotonin, IPA), phenyl derivatives (phenylalanine, tyrosine, hippuric acid, phenyl acetyl lysine, phenyl sulfate, p-cresol sulfate, phenyl propionyl glycine, cinnamoylglycine), flavones (equol sulfate, methyl equol sulfate, others), and urate (creatinine, dihydroxyquinoline glucuronide, 12-hydroxy-5Z, 8Z, 10E, 14Z, 17Z-eicosapentaenoic acid, 3-carboxy-4-methyl-5-pentyl-2-furanpropionic acid glucuronide). The relationship between Lactobacillus spp. and the prevention of aging has been established by researchers (Caroline *et al.,* 2015).

Recent reports highlight the significant impact of the gut "microbiome" on mammalian blood metabolites (Vernocchi *et al.,* 2016; Setchell *et al.,* 1998). Notable compounds of interest include endogenous estrogens and short-chain fatty acids (SCFAs). Isoflavones are biologically transformed into endogenous estrogens by intestinal microflora. These converted estrogens are absorbed, undergo enterohepatic recycling, and reach circulating concentrations that exceed baseline levels by several orders of magnitude (del Bas *et al.,* 2018). The relationship between changes in gut microbiota and the physiological effects of the cafeteria diet (CAF) has been established by researchers (Theres *et al.,* 2014; Kumar *et al.,* 2018). Increased adiposity and altered levels of plasma leptin and glycerol are consistent with altered adipose tissue metabolism. Hepatic lipid accretion, associated with changes in microbiota, underscores the relevance of gut microbiota homeostasis in the adipose–liver axis. Genomic metabolic studies reveal that gut dysbiosis is also associated with reduced amino acid concentrations in plasma (Gómez-Guzmán *et al.,* 2015).

Impact of Gut Intoxication on the hydrodynamics of blood

Researchers have reported that dysfunctional sympathetic-gut communication is associated with gut pathology, dysbiosis, and inflammation, playing a key role in hypertension (Monica *et al.,* 2017). Observations indicate that gut dysbiosis and the reduction of butyrate-producing bacteria are associated with Angiotensin II (Ang II)-induced hypertension. Experimentally, mice treated with Ang II showed reduced hypertension and gut dysbiosis, as well as normalized intestinal Th17 cells that respond to inflammation (Seungbum *et al.,* 2016). It has been reported that gut bacteria-produced butyrate plays an important role in blood pressure regulation, and butyrate-producing bacteria could be considered a novel probiotic therapy for hypertension.

Numerous studies have recently explored the impact of gut microbiota on hypertension. Notably, in a classical experiment with germ-free rats, elevated blood pressure was observed, implicating the role of gut microbiota in its regulation (Honour, 1982; Mell *et al.,* 2015; Yang *et al.,* 2015; Qi *et al.,* 2015; Adnan *et al.,* 2017). Yang *et al.,* (2015) observed significant dysbiosis, characterized by decreases in microbial richness, diversity, evenness, and an increased Firmicutes/Bacteroidetes ratio in hypertensive animals (Susanne *et al.,* 2016). Additionally, researchers have reported that gut microbiota participates in Angiotensin II-induced vascular dysfunction and hypertension (Luisa *et al.,* 2016). Furthermore, a significant number of butyrate-producing bacteria (Odoribacter) is associated with lower blood pressure overnight in pregnant women (Kawase *et al.,* 2000). The application of *Lactobacillus* as probiotics in regulating hypertension has also been reported by researchers (Pluznick *et al.,* 2013; Evans *et al.,* 2013).

Indirect evidence also supports the role of short-chain fatty acids (SCFAs). SCFA production has been considered a signal from gut microbiota and has been reported as a modulator of blood pressure (Pluznick *et al.,* 2013), and disease susceptibility (Pluznick, 2013). It has been shown that SCFAs can excite host G-protein coupled receptor (GPR) pathways, altering renin secretion and regulating hypertension (Sharkey *et al.,* 2014). Experiments on renal and vascular olfactory receptor Olfr-78 and GPR41 knockout mice revealed their roles in blood pressure modulation. Blood pressure is raised by stimulation of Olfr-78, while a decrease is reported by stimulation of GPR41 (Felix *et al.,* 2015).

Additionally, researchers have highlighted the link between the gut enteric nervous system and the central nervous system in regulating blood pressure (Min and Rhee, 2015). Products of gut fermentation are also related to the activation of the sympathetic nervous system and lymphocyte trafficking in the intestine (Hartiala *et al.,* 2014; Sharma *et al.,* 2019).

Another line of research linking gut microbiota and hypertension comes from molecular studies. Researchers have reported that 10% of the host's transcriptomes can be regulated by gut microbiota, modulating immunity, cell proliferation, and metabolism (Cluny *et al.,* 2012; Jones *et al.,* 2008). Various byproducts formed by gut microbiota include p-cresol, indoxyl sulfate, and TMAO. Elevated TMAO plasma levels have been said to be determined by genes (Schnabl and David, 2014). Observations by Sharma *et al.,* (2019) showed that inhibition of microglial activation alone was sufficient to induce significant antihypertensive effects through unique changes in gut microbial communities and a profound reduction in gut pathology. This research initiated a link between microglia and certain microbial communities that may have implications for the treatment of hypertension (Sharma *et al.,* 2019).

In light of existing research, it is now well-established that the Gut-Liver Axis (GLA) plays a significant role in extra-intestinal disorders, including hypertension. However, the current mode of treatment primarily focuses on managing blood osmotic pressure by removing salts from the body through the kidneys. Additionally, the continuous use of daily medications, which can affect fat metabolism, often leads to obesity over time.

Therefore, it seems logical to modulate gut microbiota, either through dietary interventions or the use of probiotics. Nevertheless, before implementing such approaches in human subjects, it is crucial to have a well-defined plan of action for modulators and a clear understanding of the mechanisms through which they operate. Furthermore, additional research is necessary to elucidate the precise mechanisms by which gut fermentation is modulated at different metabolic levels.

Limitations

1. **Need for Verification**: The discussed hypotheses on gut microbiota's role in hypertension and diabetes require rigorous validation through future research.
2. **Focused Scope**: Primarily addresses hypertension and diabetes, which may limit the applicability to other conditions influenced by gut microbiota.
3. **Implementation Details**: Further guidance on the practical application of suggested therapies would enhance clinical relevance.
4. **Mechanistic Gaps**: More research is needed to fully understand the specific mechanisms by which gut fermentation and microbiota influence metabolic pathways.

Author Contributions

Alok Tripathi: Investigation, formal analysis, writing—original draft.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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