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Letter to Editor

Efficacy and Challenges in Usage of Gut Microbiome in Management of Hypertension

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Sir,

Hypertension is a major risk factor for cardiovascular and cerebrovascular diseases and leads to target organ damage including myocardial infarction, stroke, heart failure, and renal disease. Around 1.5 billion people worldwide have hypertension, and it is estimated that it causes about 8 million deaths per year. Although there are several drugs available to lower Blood Pressure (BP), a large proportion of treated patients do not reach the BP targets recommended by current guidelines.[1] Non-pharmacological interventions to prevent and treat hypertension are lifestyle modifications, such as increased physical activity, yoga/pranayama, reduced salt and alcohol intake, quitting smoking, weight loss, and a healthy diet with high fiber content. Additionally, gut microbiome, which is quite diverse, also has potential influence on blood pressure.[1,2]

Gut microbiome are commercially available as probiotic supplements, which are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". Probiotics are known to have potential role in different diseases. For example, probiotic administration is useful in acute infective diarrhea, irritable bowel syndrome, causes reduction of cholesterol levels, attenuates hypertension, myocardial hypertrophy, and heart failure after myocardial infarction.[2,3]

Certain metabolites of gut microbiome like Short Chain Fatty Acids (SCFAs), bile acids, Hydrogen Sulphide (H_2S) can decrease blood pressure by dilating peripheral blood vessels, maintaining vascular endothelial function, improving insulin sensitivity, lowering blood lipids, reducing inflammatory response, decreasing heart rate, inhibiting the sympathetic nervous system, and protecting kidney function, while other metabolites Trimethyl Amine-Oxide (TMAO), Lipopolysacharides (LPS) can increase blood pressure by constricting blood vessels, increasing inflammatory response, damaging vascular endothelial function, and exacerbating atherosclerosis.[2-4]

Foods rich in fibers like fruits, vegetables, and grains, promote growth of SCFA-producing gut microbiota including Bifidobacterium lactis, lactobacillus rhamnosus, lactobacillus casei, lactobacillus helveticus, lactobacillus paracasei, Coprococcus, Butyrivibrio, and Anaerobutyricum soehngenii species have demonstrated modest blood pressure lowering effects in humans. On the other hand, foods rich in red meat, promotes growth of gut microbiota like Anaerococcus hydrogenalis, Clostridium asparagiformis, Clostridium hathewayi, Clostridium sporogenes, Desulfovibrio desulfuricans, and Escherichia fergusoni, which convert choline, phosphatidylcholine, lecithin, and L-carnitine, into Trimethyl Amine (TMA) and TMAO. TMAO acts as a risk factor for the development of hypertension by affecting renin-angiotensin system. High salt intake also has shown increased plasma concentration of TMAO, due to gut dysbiosis in rats.[2-5]

In animal studies, beef feeding increased the relative abundance of Firmicutes, while decreasing Bacteroidetes. Increased Firmicutes/Bacteroidetes ratio, is often associated with increased BMI (body mass index) in human subjects and increased BMI is positively associated with increased blood pressure.[1,5]

Recently innovative research conducted by Xue mei *et al*, tested Lactobacillus paracasei, a beneficial gut bacterium, that was specially modified to produce a protein called ACE2 in laboratory rats that are predisposed to hypertension and unable to naturally produce ACE2, demonstrated lowering of blood pressure.[6]

A meta-analysis suggested a beneficial effect of probiotics on BP by a modest degree, especially in the diabetes mellitus and hypertension. However, prolonging the duration of treatment could not improve the beneficial antihypertensive effect.[7] The effects of gut microbiota on BP, whether beneficial or harmful, are influenced by multiple factors including genetics, epigenetics, lifestyle choices, microbiome strain or species, and antibiotic usage. Probiotics available as supplements often contain mixed cultures of live microorganisms rather than single strains. With the increase of age, baseline Body Mass Index (BMI), treatment duration, and systolic BP, the effects of probiotics on BP are still

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unknown. All these factors collectively contribute to overall control of blood pressure.[3,4]

Even though there is plethora of scientific literature available regarding the role of gut microbiome in hypertension, but till date, there is neither clarity nor established guidelines and consensus regarding strain-specificity for hypertension in any of the existing national and international guidelines like European Society of Hypertension (ESH), International Society of Hypertension (ISH) etc. Innovative microbiome-based or targeted medication related research, which have the potential to revolutionize the treatment of hypertension are highly recommended in future because effects of probiotics can be specific to certain probiotic species and strains. Recommendations for their use in the clinical practice or in research studies need to be compulsorily species and strain specific and interpretation of data from studies involving mixture of probiotic supplements can be misleading in terms of beneficial effects, efficacy and safety and should be cautious.

ABBREVIATIONS

BP: Blood Pressure; **SCFA:** Short Chain Fatty Acids; **H2S:** Hydrogen Sulphide; **TMAO:** Trimethyl Amine- Oxide; **LPS:** Lipopolysacharides; **TMA:** Trimethyl Amine.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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