
IN THE NAME OF GOD

# Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies

## Introduction

Hypertension (HTN) is a common disorder that affects a large heterogeneous patient population and which has major pub- lic health and economic implications

By 2025, the total number of hypertensive patients is expected to increase to 1.56 billion globally [1].

HTN is the leading cause of :

cardiovascular and renal diseases, including stroke, heart failure, coronary heart disease, and chronic kidney disease

HTN is estimated to affect more than one billion people worldwide. It accounts for 13% of all deaths, and seven mil- lion premature deaths per year

Similar to other disease states, idiopathic HTN is called ‘essential’ or ‘primary’ when its exact cause and pathophysiology are unknown. Known, direct causes of HTN are identified in only 5—10% of all cases and are designated as ‘secondary’ owing to a precise underlying pathophysiological mechanism

Although studies on genetic predisposition to HTN have implicated genes (e.g., *M235T*, *T174M*, *ATP2B1*, *GNB3*, NOS3) [5—8], the etiology of systemic inflammation still needs to be further discussed.

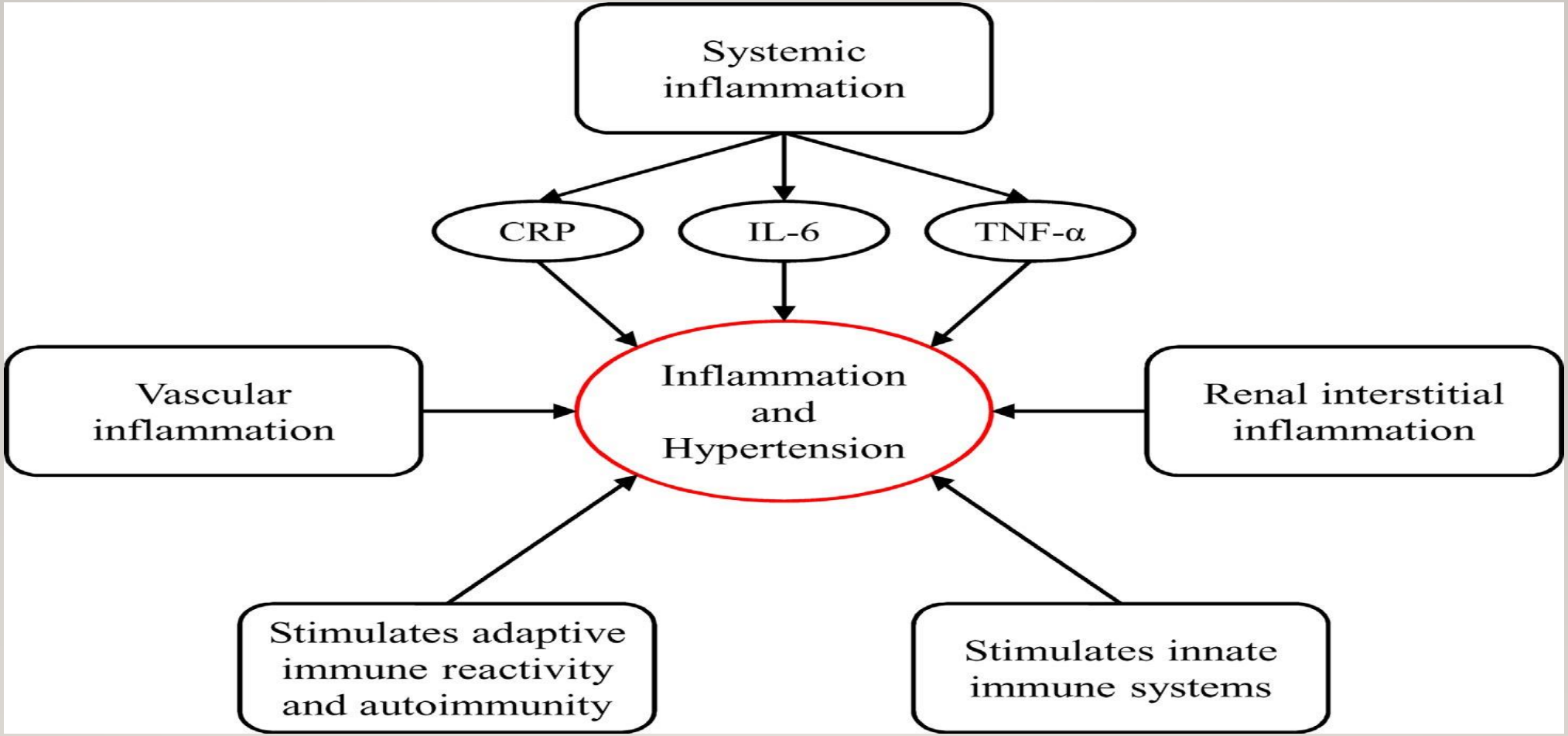



**Figure 1** Potential association between inflammation and hypertension. CRP: C-reactive protein; IL-6: interleukin-6; TNF-□ : tumor necrosis factor-□

There is a huge population of resident microbes in the intestine of an individual [10,11].

These organisms play a vital role in human health and simultaneously provide critical sig- nals for the development of host immunity.

Recent studies in animal models and human subjects have revealed that dysbiosis of the gut microbiota is associated with HTN pro- gression [12—15].

Changes in the abundance of some gut microbial strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation, and they may be biomarkers for HTN prevention and treat- ment.

Though still a relatively nascent field of research, evidence to date suggest that the gut microbiome may represent fertile targets for prevention or management of HTN.

In this review, we summarize recent literature to help further understand how the alteration of gut microbiota composition contributes to HTN.

# The role of gut microbiota in hypertension pathogenesis

## Hypertension pathogenesis

HTN is the most common chronic disease characterized by a sustained systolic blood pressure (BP) value of ≥ 140 mmHg and a diastolic pressure of ≥ 90 mmHg (140/90) in young persons.

Meanwhile, BP increases with age and hence only elderly people ≥ 60 years with BPs above 150/90 mmHg may require treatment [16].

The pathogenesis of HTN is complex.

HTN-related genes such as *M235T*, *T174M*, BMPR2 and *GNB3* [5,17,18], and environmental factors have also been shown to contribute to disease pathogenesis.

Changes in vascular structure and function are critical processes in the pathologies and include endothelial dysfunction, altered contractility, and vascular remodelling [19,20].

A number of pathways such as the fluid and electrolyte balance pathway, the renin-angiotensin system (RAS), the kinin-kallikrein system, the neutral endopeptidase system, and the endothelin-converting enzyme system are known to control human BP

There are also other possible mechanisms (Fig. 2), i.e., that gut microbiota can influence the production of various hormones such as serotonin, dopamine, and norepi-nephrine which can affect BP.

In addition, the metabolites of gut microbiota such as p-cresol sulfate, indoxyl sulfate, trimethylamine N-oxide (TMAO), and short chain fatty acids (SCFAs) can profoundly affect the cardiovascular system [13].

The intestinal bacteria have profound effects on the hosts' biology including the ability of the kidney to excrete sodium load and regulate blood pressure [22,23].

Previ- ous study had found that chronic kidney disease patients have elevated plasma levels of TMAO [24,25]. This ele- vation in plasma TMAO levels maybe mainly due to gut microbial action.

SCFA produced by the gut microbiota [26] influence blood pressure that is related to renal sensory nerves [27,28].

These SCFAs activate two orphan G protein- coupled receptors, GPR41 (also known as Free Fatty Acid Receptor 3), GPR43 (also known as Free Fatty Acid Recep- tor 2), and olfactory receptor 78 (Olfr78) that can regulate blood pressure.

Low-grade inflammation can be the result of gut microbial action [30].

Thus, intestinal microbiota appear to contribute to the development of HTN by inducing chronic inflammation and generating reactive metabolites.

The alteration of gut microbiota has an important impact on the immune system.

Gut micriobiota
Serotonin, Dopamine, and Norepinephrine
P-cresol sulfate, Indoxyl sulfate, and TMAO
Sodium metabolism
Inflammation
SCFA
GPR43
GPR41
Olfr78
Blood pressure

# The role of gut microbiota in hypertension

Recently, it was indicated that gut microbial triggers have been implicated in HTN [12]. The vast majority of these stud- ies suggested that the subjects with HTN exhibit alterations in the relative abundance of “beneficial” and potentially “harmful” bacteria compared to healthy subjects

There is convincing evidence from both human and ani- mal studies suggesting that different kinds of factors (e.g., diet, level of physical activity, pregnancy, and use of antibi- otics) are related to HTN via affecting gut microbiota.

In comparison with healthy controls, gut micro- bial richness, diversity, and evenness significantly decreased in spontaneously hypertensive rats, angiotensin II-induced HTN in rats, and small group of humans with essential HTN [31].

In addition, the *Firmicutes* and *Bacteroidetes* ratio increased and the abundance of acetate- and butyrate- producing bacteria decreased [31].

The oral administration of minocycline normalized the *Firmicutes* and *Bacteroidetes* ratio and blood pressure of spontaneously hypertensive rats and rats with angiotensin II-induced HTN [31].

Durgan et al. [32] also found that obstructive sleep apnea (OSA) rat fed a high-fat diet had significant increase of blood pressure compared with OSA rat fed normal chow diet.

This findings was relation to significant alterations of the gut microbiota, including decreases in bacterial taxa known to

produce the short chain fatty acid butyrate.

Furthermore, transplant of dysbiotic cecal contents from hypertensive OSA rats on high-fat diet into OSA recipient rats on normal chow diet (shown to be normotensive) resulted in HTN sim- ilar to that of the donor.

Adnan et al. [33] have shown that normotensive WKY rats transplanted with spontaneously hypertensive stroke prone rats microbiota have significant increase of systolic blood pressure (SBP) and *Firmicutes* and *Bacteroidetes* ratio compared to those cecal content from normotensive WKY rats.

Furthermore, relative abundance of multiple taxa correlated with SBP. In keeping with this observation, a recent experiment investigated the micro- biome of Dahl salt-sensitive (S) and Dahl salt-resistant (R) rats [34].

The abundance of phylum *Bacteroidetes*, espe- cially the S24-7 family, and the family *Veillonellaceae* of the *Firmicutes* phylum significantly increased in the Dahl salt-sensitive S rats compared with the Dahl salt-resistant R rats.

Dahl salt-sensitive rats transplanted with salt-resistant rat microbiota had higher blood pressure, higher plasma acetate and heptanoate, lower the family *Veillonellaceae*, lower sodium excretion, and shorter lifespan than those that received cecal content from Dahl salt-sensitive rats.

There- fore, these accumulating studies suggest that changes in the composition of gut microbiota play a significant role in induction and furthering the progression of HTN.

Pluznick et al. [27] reported that olfactory receptor 78 (Olfr78) is expressed in the renal juxtaglomerular appara- tus, where it mediates renin secretion in response to SCFA

In addition, both Olfr78 and G protein-coupled receptor 41 (Gpr41), another SCFA receptor, are expressed in smooth muscle cells of small resistance vessels.

Propionate, a SCFA shown to induce vasodilation ex vivo, produces an acute hypotensive response in wild-type mice. This effect is dif- ferentially modulated by disruption of Olfr78 and Gpr41 expression.

SCFAs are end products of fermentation by the gut microbiota and are absorbed into the circulation. Antibiotic treatment reduces the biomass of the gut micro- biota and elevates blood pressure in Olfr78 knockout mice. Thus, SCFAs produced by the gut microbiota modulate blood pressure via Olfr78 and Gpr41.

Recently, A research was completed in China that examined the composition and function of gut microbiota in 196 participants of healthy control, pre-hypertension (pHTN) and HTN by 16s Metage-nomic sequencing [35]. Compared to the healthy controls, microbial richness and diversity dramatically decreased in both pHTN and HTN groups.

Furthermore, *Prevotella* and

*Klebsiella* were overrepresented in individuals with pHTN or HTN. *Porphyromonas* and *Actinomyces*, which were also elevated in the HTN group.

By contrast, *Bacteroides*, *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, *Coprococcus*, and *Butyrivibrio*, which were enriched in healthy controls, declined in pHTN and HTN patients. these bacteria are known to be essential for healthy status

*Fae- calibacterium* and *Roseburia* are crucial for butyric acid production [36,37].

Moreover, *Bifidobacterium* is an impor- tant probiotic influencing intestinal microbial homeostasis, gut barrier, and lipopolysaccharide (LPS) reduction [38].

The authors took gene functional annotation, further found functional alteration in gut microbiota of pHTN and HTN. The thirty-nine modules decreased in pHTN and HTN groups were involved in branched-chain amino acid biosynthesis and transport, ketone body biosynthesis, two-component regulatory system, and degradation of methionine and purine. These metabolic functions are essential for the host and have been observed in healthy populations [38—41].

In addition, seventeen modules elevated in pHTN and HTN, including LPS biosynthesis and export, phospholipid transport, phosphotransferase system (PTS), biosynthesis of phenylalanine and phosphatidylethanolamine, and secretion system.

endogenous compounds whose levels significantly decreased in pHTN and HTN include phosphatidylserine (PS), 3,4,5-trimethoxycinnamic acid, lysophosphatidyl-choline (LysoPC), S-carboxymethyl-L-cysteine, and lysophos- phatidylethanolamine (LysoPE). 3,4,5-Trimethoxycinnamic acid is capable to protect against inflammatory diseases through suppressing cell adhesion molecules in vascu- lar endothelial cells [42].

Also S-Carboxymethyl-L-cysteine exerts anti-inflammatory properties [43].

On the other hand, endogenous compounds whose levels significantly increased in pHTN and HTN include metabolites such as N□ -acetyl-L- arginine, stearic acid, phosphatidic acid (PA), and glucoside.

there was a positive association between 9,10-dichloro-octadecanoic acid (stearic acid) and microflora including *Klebsiella*, *Prevotella*, and *Enterbacter*, which were all overrepre-sented in HTN.

Thus, a disease classifier based on microbiota and metabolites may be constructed to discrim- inate pre-hypertensive and hypertensive individuals from controls accurately.

At last, by fecal transplantation from hypertensive human donors to germ-free GF C57BL/6L mice, elevated blood pressure was observed to be transferable through microbiota [35].

Above all, alterations in gut microbiota and colonization by opportunistic bacteria may boost the risk of developing HTN. And early intervention for pre-HTN is very important.

# Probiotics therapy

Probiotics are widely studied in medical application to pre- vent or treat many diseases, such as rheumatism arthritis, diabetes, obesity, allergies and asthma [44–46].

A great number of studies have testified that modulating gut microbiota may be an effective strategy to cure and maintain HTN (Fig. 3). The therapeutic effects of probiotics on HTN have also been confirmed in animal and humans.

*Lactobacilli* can not only enhance release of anti-inflammatory factors [47—49], but also appear to protect against invasion of pathogenic bacteria [50].

A random- ized placebo-controlled study shown that *Lactobacillus helveticus* LBK-16H fermented milk containing bioactive peptides in normal daily use has a blood pressure-lowering effect in hypertensive subjects [51].

Ahrén et al. [52] also demonstrated the supplementation of *L. plantarum* DSM 15313 fermented blueberries can significantly reduce sys- tolic and diastolic BP in hypertensive rat model treated with nitro-L-arginine methylester (L-NAME).

Mechanistically, it has been suggested that fermentation of blueberries by *L. plantarum* could reduce BP trough a mechanism involv- ing a nitric oxide (NO)-dependent pathway.

In another research, oral of administration recombinant *L. plantarum* expressing angiotensin converting enzyme inhibitory peptide significantly decreased systolic blood in the model of spontaneously hypertensive rats (SHR) [53].

Furthermore, this finding was linked to an increased level of nitric oxide (NO), decreased levels of endothelin (ET) and angiotensin II (Ang II) in plasma, heart, and kidney, as well as a dra- matically decreased triglyceride level.

Aoyagi et al. [54] found that the risk of developing HTN is substantially lower in elderly people who take fermented milk products containing *L. casei* strain Shirota (LcS) at least 3 times a week.

The results of these study indicated that *Lactobacilli* can play a protective role in the development of HTN.

A mixture of probiotics has also been used for the treatment of HTN.

ACE inhibition, in turn, lowers the synthesis of angiotensin II, which result in attenuation of vasoconstric tion and blood pressure.

Gómez-Guzmán et al. [57] demonstrated that the long-term oral administration of probiotics *L. fermentum* CECT5716 (LC40), or *L. coryniformis* CECT5711 (K8) plus *L. gasseri* CECT5714 (LC9) (1:1) mixture significantly reduced the cardiac and renal hypertrophy in spontaneously hypertensive rats (SHR).

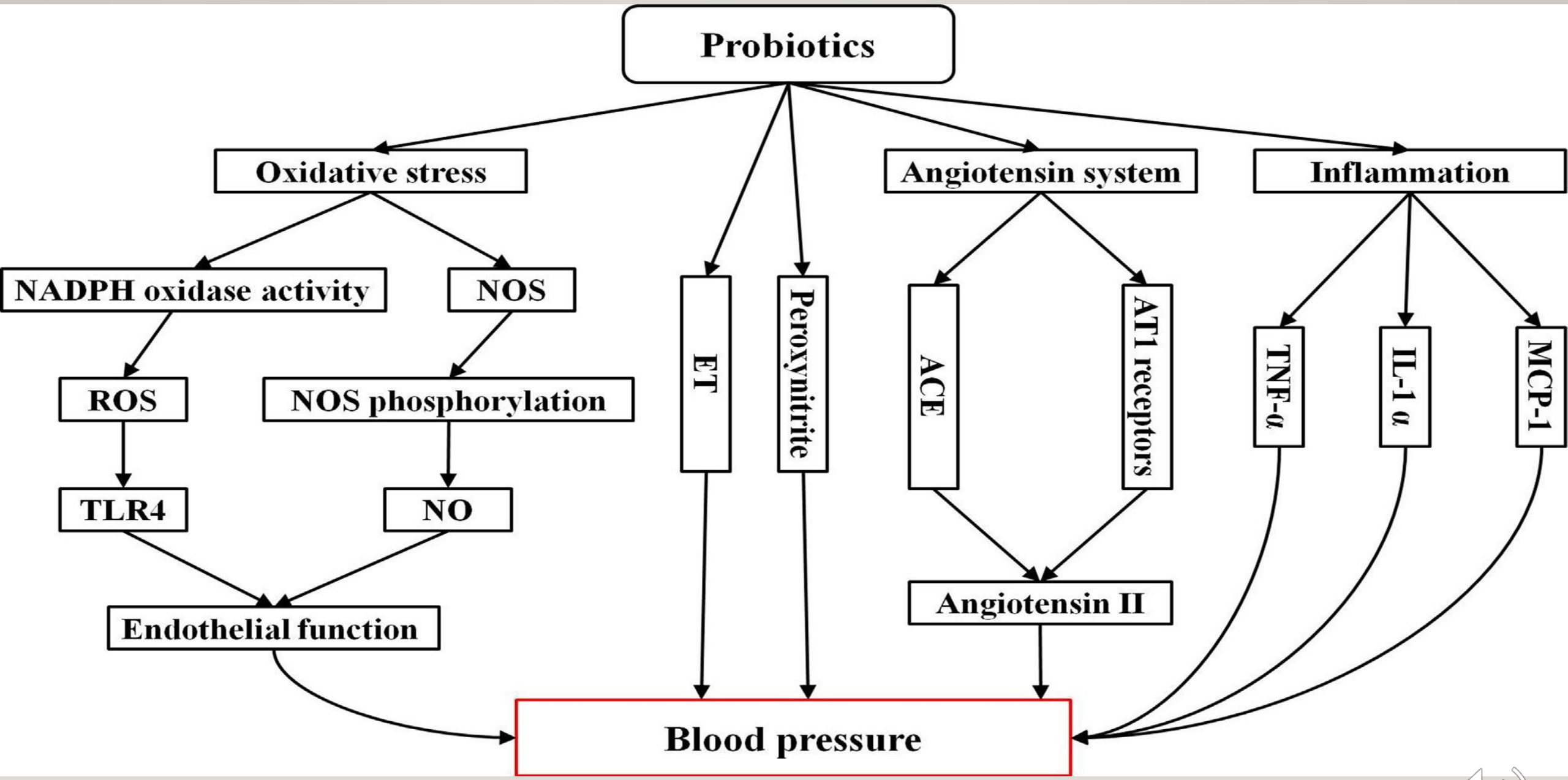
This finding was linked to improved aortic endothelium dependent relaxation to acetylcholine, decreased aortic superoxide levels by reducing the increased toll-like receptor-4 (TLR- 4) mRNA levels and NADPH oxidase activity, and increased endothelial nitric oxide synthase phosphorylation.

Thus, probiotics exert cardiovascular protective effects in genetic HTN related to the improvement of endothelial function, vascular pro-oxidative and pro-inflammatory status.

Fur- thermore, Probiotic treatments induced a change in the cecum microbiota of SHR, with higher counts of the *Lac- tobacillus* spp. cluster, and lower counts of *Bacteriodes* spp. and *Clostridium* spp.

Above all, probiotics intervention might be a potential effective approach in the treatment of HTN through restoring gut microbiota.

Therapies that may most efficiently bring the disease under control are still being sought.


Probiotics
Oxidative stress
Angiotensin system
Inflammation
NADPH oxidase activity
NOS
ET
Peroxynitrite
ACE
AT1 receptors
TNF-α
IL-1 α
MCP-1
ROS
NOS phosphorylation
TLR4
NO
Angiotensin II
Endothelial function
Blood pressure

# Concluding remark

The human gut hosts trillions microorganisms, which are collectively known as the bacterial flora.

An increasing num- ber of studies are progressively unravelling the fascinating interaction between hosts and microbiome.

Growing evi- dence suggests that gut microbiota plays a critical role in keeping health and the development of HTN.

Specific species of intestinal commensal bacteria may exert either a protective or pathogenic influence in the development of HTN.

More clinical trials with larger sam- ple sizes should be conducted to identify the alterations of microorganism species in hypertensive subjects.

What we think is far more important is how intestinal microbiota alters blood pressure and vascular function and whether or not the genetics of intestinal microbiota takes part in the pathophysiology of HTN.

Probiotics can confer health benefits
by mod- ulating the composition of
gut microbiota to restore the  physiological bacterial flora.

Many investigations have pro- vided a compelling rationale for developing the oral administration of probiotics as adjunctive therapies to HTN.

In conclusion, we have opened up an entirely new approach to the understanding and treatment of HTN and more investigations are needed in this emerging field.


Thank you

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