

ACADEMIC: REVIEW ARTICLE

Mini-review: Antihypertensive activity of probiotic *Lactobacillus casei* through modulation of the gut microbiota

Muhammad Luthfi Adnan

Abstract

Hypertension is one of the primary risk factors for cardiovascular disease, the leading cause of death worldwide. Traditional pharmacotherapy for hypertension has the potential for adverse side effects. *Lactobacillus casei* (*L. casei*) is a type of bacteria that is widely used as a probiotic in the food and biotechnology industries. This review focuses on exploring the potential of *L. casei* as an antihypertensive therapy. A comprehensive literature search was conducted with the keywords “blood pressure”, “cardiovascular disease”, “gut microbiota”, “hypertension”, “probiotic bacteria”, and “probiotics”. The identified studies reported on the antihypertensive effect of *L. casei* through its modulation of the microbiota in the gut. Although early experimental studies in mice are promising, further research at higher levels of evidence is required to corroborate the antihypertensive mechanism of *L. casei* before the probiotic can be implemented as an alternative or adjunct treatment for hypertension.

Keywords: blood pressure, gut microbiota, hypertension, probiotic bacteria.

Introduction

Hypertension is one of the most common diseases in the world and is a major risk factor for cardiovascular disease.¹ Based on data from the World Health Organization (WHO), hypertension and its complications are the cause of 9.4 million deaths each year, and this mortality rate will increase the number of deaths due to hypertension and its complications from 17% of all deaths in 2008 to 24% by 2030.² Risk factors for hypertension include increasing age, obesity, smoking, sedentary lifestyle, and socioeconomic conditions in low- and middle-income countries (LMIC).^{3,4}

Treatment of hypertension can include pharmacological therapies, such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics, and β -blockers.⁵ However, the need for long-term pharmacotherapy can increase the risk of non-compliance.⁶ Compliance with treatment is important for reaching the target blood pressure. Non-compliance can lead to a lack of control of blood pressure and its other, and sometimes life-threatening, cardiovascular complications.⁷ Thus, blood pressure-lowering agents with less side effects compared to current drugs would be useful to offer patients.⁸ Of note, several recent studies have shown benefits in providing probiotics as a dietary supplement to reduce the risk of cardiovascular disease.⁹

Lactobacillus casei (*L. casei*) is one of the bacteria in the *Lactobacillaceae* family, and has a relation with the *L. paracasei* and *L. rhamnosus* species. Much research on *L. casei* has been on its use in the commer-

cial food industry due to its health potential.¹⁰ Several experimental models and clinical trials have shown the health effects of *L. casei* include lowering cholesterol levels, improving immune system function, and preventing obesity and the metabolic syndrome.¹¹ Several recent studies have shown that the antihypertensive effect of *L. casei* is exerted through the modulation of other intestinal microbiota.¹² This review aims to discuss the relationship between gut microbiota and hypertension, and the antihypertensive effects of *L. casei*.

Methods

A comprehensive literature search was conducted between January–April 2020 using the Google Scholar and PubMed search engines. The literature search used the keywords “blood pressure”, “cardiovascular disease”, “gut microbiota”, “hypertension”, “probiotic bacteria”, and “probiotics”. The inclusion criteria used to select sources for this literature review were studies available in full text, written in English, and that had been published within the last 10 years or that were published more than 10 years ago but support other more recent literature sources.

Results

PATHOPHYSIOLOGY OF HYPERTENSION AND ITS RELATIONSHIPS TO GUT MICROBIOTA

The pathophysiology of hypertension is influenced by impaired regulation of blood pressure through the renin-angiotensin-aldosterone system (RAAS).¹³ RAAS affects the activity of the Na⁺/K⁺-ATPase channel, which plays a role in the reabsorption of water and sodium in the kidney tubules, and regulates blood volume through vasoconstriction of vascular smooth muscle cells.¹⁴ Disorders of RAAS can trigger pathophysiological tubular reabsorption of salt and water through stimulation of the renal sympathetic nervous system. This increases sodium reabsorption, triggering renin activation, which breaks down angiotensinogen to angiotensin I (AT-I), which is further broken down by an enzyme that converts angiotensin to angiotensin II (AT-II). AT-II triggers vasoconstriction of blood vessels¹⁵ and also triggers the release of aldosterone from the adrenal glands which further increases the reabsorption of water and salt.¹⁶

The RAAS system also affects the resistance of blood vessels by interfering with the function of nitric oxide (NO), which acts as a vasodilator and antagonist to AT-II function.¹⁷ In hypertensive conditions, NO is deficient, resulting in vessel stiffness.¹⁸ This deficiency occurs in hypertensive conditions due to the activation of RAAS, triggering the production of asymmetric dimethylarginine (ADMA), which can inhibit NO synthase activity, resulting in reduced NO.¹⁹ NO deficiency results in loss of nephrons, higher glomerular capillary pressures,



Figure 1. Proposed mechanisms of *Lactobacillus casei*-mediated antihypertensive effect.

and glomerular hyperfiltration, which, in turn, leads to decreased sodium reabsorption, further increasing RAAS activity and leading to hypertension.²⁰ Also, the increased production of AT-II results in an increased inflammatory response that results in vascular dysfunction.²¹ Furthermore, NO deficiency causes renal ischaemia and subsequent chronic kidney disease, which is another risk factor for cardiovascular disease.¹⁸ Importantly, NO deficiency can be influenced by gut dysbiosis-producing lipopolysaccharide (LPS) and also by oral microbiota, which colonise the intestine, resulting in inflammation and oxidative stress on NO formation.^{22,23}

Experimental and clinical studies have demonstrated that there are different gut microbiota in normal and hypertensive subjects.^{24,26} These changes in microbiota, mainly an increase in *Firmicutes* and *Bacteroidetes*, were associated with higher blood pressures.²⁴ An increase in *Firmicutes* and *Bacteroidetes* is a marker of dysbiosis, and results in oxidative stress and impairs NO function.²⁴ The regulation of gut microbiota is influenced by the activity of olfactory receptors 78 (Olf78) expressed in the renal juxtaglomerular apparatus, and G protein-coupled receptor 41 (Gpr41) expressed in smooth muscle cells in blood vessels.²⁵ Further studies are required to explain the causative relationship between dysbiosis and hypertension, and may make modulation of gut microbiota with probiotics a target for the treatment of hypertension.^{24,26}

LACTOBACILLUS CASEI PROBIOTIC BACTERIA AS AN ANTIHYPERTENSIVE AGENT

Probiotic bacteria are defined by the Food and Agriculture Organization (FAO) as living microorganisms which, when consumed in sufficient quantities, provide health benefits to the host.²⁷ *Lactobacillus casei* is one of the probiotic bacteria of the genus *Lactobacillus* that comes from the family *Lactobacillaceae*. The *Lactobacillaceae* family has been used extensively as a food product and in various fields in pharmacotherapeutics and biotechnology.²⁸ *L. casei* has been studied extensively because it has the most significant antimicrobial effect on Gram negative and Gram positive bacteria, and a high survival ability in dealing with the environmental stresses of the gastrointestinal tract.²⁹

There have been several studies conducted to examine the antihypertensive effects of *L. casei*, in both experimental mouse models and human clinical trials.³⁰ One such study demonstrated that supplementation with *L. casei* reduced blood pressure and mean arterial pressure after eight weeks of administration in hypertensive rats.³¹ The study also demonstrated improved blood vessel dilation function in hypertensive rat subjects, which was followed by increased glutathione and NO activity.³¹ The authors propose that inhibition of the formation of the antioxidant glutathione results in oxidative stress in blood vessels, leading to stiffness and, consequently, hypertension. The antioxidant effect of *L. casei* is therefore likely to occur by enhancing glutathione and NO levels, which contribute to the antihypertensive effect.^{31,32}

Another study also showed a lower incidence of hypertension in the elderly Japanese population with consumption of fermented milk containing the *L. casei* Shirota strain (LcS) ≥ 3 times per week, compared to populations with lower consumption levels.³³ However, this study is limited by its retrospective and observational study design, with the control group limited to subjects with consumption ≤ 3 times per week, and the absence of subjects who did not take any probiotics.³³ Also, the risk factors for hypertension are numerous, including salt intake, lifestyle, and genetics; and their confounding roles have not been investigated in these studies.^{33,34} In another study, the *L. casei*-mediated antihypertensive effect was associated with beneficial effects on glucose and lipid metabolism.³⁵ Thus, further studies are needed regarding the antihypertensive activity of *L. casei* in larger and more heterogeneous populations.

ANTIHYPERTENSIVE MECHANISM OF LACTOBACILLUS CASEI

Proposed mechanisms are summarised in Figure 1. The antihypertensive activity of *L. casei* is associated with the higher production of short-chain fatty acids (SCFAs) through modulation of gut microbiota.^{36,37} SCFAs are widely-studied bacterial metabolites produced by the fermentation of complex polysaccharides, including resistant starches and some of types of fibre, in the colon. SCFAs consist of acetate, propionate, and butyrate, which are widely present in the colonic epithelium.³⁸ *L. casei*-produced SCFAs are thought to modulate other gut microbiota and exert their antihypertensive effect through Olf78 and Gpr41 receptors expressed in smooth muscle cells.²⁵ At Gpr41 receptors, propionate can inhibit the increase in blood pressure through vasodilatory activity in the kidney, and generate a hypotensive response, while the receptor Olf78 act as support to counter powerful hypotension.^{25,39} The interaction of acetate and propionate at the Gpr41 receptor reduces the stimulation of renin secretion in the juxtaglomerular apparatus.⁴⁰ Butyrate counteracts some effects of AT-II, which can prevent AT-II-mediated endothelial dysfunction.⁴¹

Several other studies have demonstrated an association between SCFAs and blood pressure. One study showed that increasing acetate levels through increasing fibre intake can lower blood pressure while reducing left ventricular hypertrophy in a hypertensive mouse model.⁴² This study showed that acetate activity from gut microbiota after a high-fibre diet had blood pressure-lowering and cardioprotective effects associated with the inhibitory activity of interleukin-1 (IL-1).⁴² Inhibition of IL-1 can reduce fibroblast activity and decrease cardiac fibrosis, which are hallmarks of ventricular hypertrophy and kidney damage and result in hypertension.⁴³

Another mouse study has demonstrated the antihypertensive activity of propionate through another anti-inflammatory effect.⁴⁴ Propionate-mediated attenuation of the systemic T-cell response to AT-II activity was seen to reduce cardiac hypertrophy and endothelial dysfunction, which leads to the pathophysiological formation of

atherosclerotic lesions and increases the risk of heart failure.⁴⁴ Thus, propionate-mediated effects on AT-II activity in hypertension could potentially protect against cardiac and vascular damage and reduce the risk of atherosclerosis and coronary heart disease.^{44,45}

The antihypertensive effect of butyrate is mediated through interaction with colonocytes, where butyrate improves the gut epithelial barrier.⁴⁶ Butyrate is thought to exert an anti-inflammatory effect through reducing the release of proinflammatory LPS that causes gut dysbiosis.⁴⁷ LPS is thought to interfere with NO production and mediate endothelial dysfunction, which play a role in the progression of hypertension.⁴⁷ An experimental study has demonstrated an association between butyrate and reduced blood pressure, likely through improving the gut epithelial barrier, preventing LPS from translocating to the circulation, and changing the gut microbiota population, which can influence vascular and cardiac function.⁴⁸ However, further research is required to completely explain the antihypertensive mechanism of *L. casei* and the effect of its SCFA metabolites.

Conclusion

Hypertension is a major cause of premature death worldwide and is a major risk factor for serious cardiovascular diseases. At present, there is a relationship between the gastrointestinal microbiota and hypertension. Recent studies have shown that consumption of the *L. casei* has an antihypertensive effect in primarily experimental mouse studies and one human trial. *L. casei* is thought to modulate the gut microbiota through SCFA metabolites, thereby lowering blood pressure via an incompletely understood mechanism. Further research is needed to confirm the promise of *L. casei* as an antihypertensive for clinical use.

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About the author

> Muhammad Luthfi Adnan is a fourth-year medical student from Universitas Islam Indonesia. He has an interest in research related to the metabolic syndrome. In his spare time, he usually spends time watching and writing about movies.

Correspondence

Muhammad Luthfi Adnan: luthfiadnan35@yahoo.co.id