World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Antihypertensive Effect of Probiotics

Sasikala Sasikumar[1] and Kannan Eagappan[2]

Research Scholar[1] and Associate Professor[2], Department of Clinical Nutrition and Dietetics, PSG College of Arts and Science, Coimbatore, India

Received: 22-07-2014 / Revised: 02-08-2014 / Accepted: 21-08-2014

ABSTRACT

Hypertension is a major health problem worldwide. Optimizing blood pressure control has been shown to improve overall health outcomes. Besides pharmacological therapies, non pharmacological approach such as dietary modification using Probiotics play an important role in controlling blood pressure. Probiotics are live organisms that are primarily used to improve gastrointestinal disorders such as diarrhoea, irritable bowel syndrome, constipation, lactose intolerance, and to inhibit the excessive proliferation of pathogenic intestinal bacteria. However, recent studies have suggested that probiotics could have beneficial effects beyond gastrointestinal health, as they were found to improve certain metabolic disorders such as hypertension. This review discusses the antihypertensive roles of probiotics in controlling blood pressure.

Keywords: Probiotics, hypertension, angiotensin-converting enzyme, renin-angiotensin system

INTRODUCTION

The World Health Organization defines probiotics as "live microorganisms" which when administered in adequate amounts confers a health benefit on the host[1]. Various microorganisms have been found to posses such properties, while Lactobacillus and Bifidobacterium are the most common probiotic bacteria used as food adjuvant. A number of gastrointestinal health benefits have been reported upon consumption of probiotic organisms, including the alleviation of diarrhoea, improvement of irritable bowel syndrome, lactose intolerance and antibacterial properties[2]. Apart from gastrointestinal integrity due to beneficial micro flora, these biological saviours do protect us from various life style disorders such as diabetes, hypertension, cardiovascular diseases, cancer etc.,
High Blood Pressure also known as the "silent killer'' affects one billion or one in three adults worldwide, and attributes to about 40% of cardiovascular related deaths; unfortunately more than 50% of hypertensive individuals are unaware of their condition[3]. American heart association defined Hypertension as a systolic blood pressure greater than 140 mmHg and or a diastolic blood pressure greater than 90 mmHg is one of the major risk factors for cardiovascular morbidities including coronary artery disease, myocardial infarction and kidney disease, as well as for mortality[4]. Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025[5]. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries[6]. There are number of factors that increase blood pressure such as obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging and perhaps sedentary lifestyle, stress, low potassium intake, and low calcium intake[7, 8]. Among these preventive factors, it is well known that dietary factors play an important role in the modulation of BP in hypertensive or normotensive individuals[9- 20]. Although the use of probiotics has been primarily associated with the improvement of gastrointestinal health, recent evidence has also shown that probiotics play an important role in other metabolic diseases leading to antihypertensive effects. Thus, this review highlights and discusses the roles of probiotics in the effort to reduce hypertension.

PATHOPHYSIOLOGY OF HYPERTENSION

Even though hypertension is the most prevalent chronic medical conditions, the patho-physiology

Corresponding Author Address: Sasikala Sasikumar, Research Scholar, Department of Clinical Nutrition and Dietetics, PSG College of Arts and Science, Coimbatore, India; *E-mail: sasikalas47@gmail.com, dtkannan@gmail.com*

of hypertensive crises is still poorly understood[21-23]. In addition, not like other disorders the hypertension develops due to a single known entity, rather multifaceted etiological factors could synergistically affect blood pressure. From the studies of Smithburger *et al* (2010) and Varon, (2008), it is clearly implicated that two processes are considered to recklessly induce hypertensive paradigm such as sudden increase in systemic vascular resistance (SVR) and a failure of cerebral blood flow auto regulation, the mechanism that maintains blood flow at an appropriate level during changes in blood pressure[22,23]. Varon, 2003 reported that hypertensive crisis can also be present without documenting any history of hypertension; the acute nature of these events suggests an underlying hypertensive condition coupled with the presence of an additional seditious factor or event[24]. This was explained by him using an example such as, in the perioperative setting, stimuli such as elevated BP during anesthesia induction, tracheal intubation, and emergence from anesthesia can be the initiating event for the hypertensive crisis [25]. Anesthesia induction alone can cause an increase of 20 mmHg in normotensive patients, and up to 90 mmHg in patients with a pre-existing hypertensive condition[26]

Studies done by Kuppasani and Reddi, 2010; Smithburger *et al.*, 2010; Vaughan and Delanty, 2000, revealed that Vascular endothelial injury may result from repeated instances of acute hypertension, associated with elevated systemic vascular resistance. As blood pressure increases, vessel walls are subjected to stress, which leads to the release of vasoconstrictors resulting in further endothelial damage[21, 22, 27]. Kuppasani and Reddi, 2010 in their study explained that If Vascular endothelial injury is not promptly treated, a cycle of clotting cascade activation, arteriole tissue death and accumulation, neurohormonal system up regulation, induction of oxidative stress, and inflammatory cytokines develops[21]. Deposition of platelets and fibrin, vasoconstriction, and thrombosis, as a consequence of vascular injury, result in decreased blood flow and supply to and from organs (hypo perfusion and ischemia) [21,22]. If this vicious cycle is not concluded, auto regulatory dysfunction becomes imminent[28.] Auto regulation is crucial to maintenance of adequate perfusion of the kidney, heart, and brain. These organs require specific amounts of oxygen to function, and reduced blood flow can lead to ischemia and organ injury. Auto regulation occurs in many body tissues, but has best been studied in cerebral blood flow. When blood pressure is severely elevated there is a right shift in the auto regulation curve, resulting in cerebral blood flow at higher mean arterial pressures[27,29 and 30.] In order to avoid hyper perfusion of tissues, blood pressure in these patients must be lowered carefully so that hypo perfusion does not occur[29, 20]

In the blood pressure range between 60 mmHg and 140 mmHg, cerebral blood flow is “auto regulated” extremely well. Belsha, 2011 explained in his study that, auto regulation in hypertensive patients occurs with mean arterial pressure (MAP) up to 180 mmHg (shifted to the right), though the blood flow remains constant. During hypertensive crises, the shift in the auto regulatory curve often fails to occur, putting patients at risk for cerebral hyper perfusion. When, the corresponding increase in BP crosses the auto regulatory range, compensatory mechanism ends[29]. Vasodilatation and endothelial dysfunction will result in cerebral fluid buildup (edema), ultimately followed by cerebral spasm (eclampsia) and ischemia[21]. Continuation of this “vicious” cycle results in the severe, acute elevation in BP.

Role of probiotics in hypertension

Blood pressure is controlled by a number of different interacting biochemical pathways. Typically, the regulation of blood pressure has been associated with renin-angiotensin system (RAS) which involves angiotensin-converting enzyme (ACE) [31]. According to Inagami, (1992) RAS regulates blood pressure, fluid and electrolyte balance. Whereas, Renin is understood to be an acid proteinase generated from the inactive precursor pro-renin by the action of kallikrein[32]. Thus, it is released whenever depletion of salt or stimulation of β2-receptors by aldosterone occurs. In RAS, renin hydrolyses plasma angiotensinogen, thus liberating the inactive angiotensin I. FitzGerald (2004) from his studies proposed out that the potent vasoconstrictor, angiotensin II is converted from angiotensin I by ACE. Inhibition of renin activity may be achieved as a result of angiotensin II production[31]. Angiotensin II can cause vasoconstriction and induce release of aldosterone and as a result increases sodium concentration and elevates blood pressure. On the other hand, ACE also contributes to the elevation of blood pressure by inactivating the vasodilator bradykinin. Therefore the levels of both angiotensin II and bradykinin allow for the regulation of blood pressure are mainly dictated by the ACE in RAS. Saito (2008) described that ACE inhibition is a key clinical target for blood pressure control, whereby ACE inhibitors can lower blood pressure by reducing the production of angiotensin II and inhibit the degradation of bradykinin[33].

The ACE inhibitory peptides are inactive within the sequence of the parent protein but can be released by microbial activity[34]. Hence, fermentation is considered to be an effective way to produce the bioactive peptides. ACE inhibitory peptides can be derived from a variety of fermented products including cheese, fermented milk, soymilk and yogurt upon fermentation by various starter microorganisms[31]. In addition to yogurt bacteria and cheese starter bacteria, probiotic bacteria have been demonstrated to produce different bioactive peptides in milk during fermentation[34]. Probiotics are able to grow in milk products because they possess a proteolytic system that degrades casein along with lactose hydrolyzing enzymes[33]. Upon fermentation, the proteinases of various probiotics are capable of releasing ACE inhibitory peptides and thus a blood-pressure lowering effect can be derived from the milk proteins[35]. Korhonen (2009) confirmed from his study that *Lactobacillus helveticus* are capable of releasing antihypertensive peptides which are ACE inhibitory tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) from milk protein casein[34]. Hence, it is imperative that milk especially after fermenting serves as a unique adjuvant in contributing ACE inhibitory tripeptides.

A study was performed by Donkor [2007] on the proteolytic activity of several dairy lactic acid bacteria cultures and probiotics as determinants of growth and *in vitro* ACE inhibitory activity in milk fermented with these single cultures. The authors reported that both *Bifidobacterium longum* and *Lactobacillus acidophilus* strains showed ACE inhibitory activity during growth[36] . This was also supported by Ong and Shah [2008], who examined the released of ACE inhibitory peptides in Cheddar cheeses made with starter lactococci and probiotics. Thus, the authors observed that cheeses made with the addition of *L. casei* and *L. acidophilus* had higher ACE inhibitory activity than those without any probiotic adjunct after 24 weeks at 4 ºC and 8 ºC, probably due to increased proteolysis. Likewise Rhyänen, (2001) confirmed that ACE-inhibitory peptides have also been found in yogurt, cheese and milk fermented with *L. casei* spp. *rhamnosus*, *L. acidophilus* and bifidobacteria strains[37] .

Recent research studies have also shown that soy peptides with inhibitory activity against ACE could be produced by fermentation with probiotics. In a study performed by Ng *et al.* [2008] to investigate the growth characteristics and bioactivity of probiotics in a tofu-based medium, both *L. fermentum* and *L. bulgaricus* strains exhibited varying proteolytic activity leading to the production of bioactive peptides with ACE inhibitory activity[38]. Additionally, Fung [2008], who evaluated growth characteristics of *L. acidophilus* in soy whey, postulated that proteolytic activity of probiotic gave rise to ACE inhibitory activity in the media. The authors also found that there was a strong correlation between the ACE inhibitory activity and growth of the probiotics. An increased growth has been associated with an increase in the *in vitro* ACE inhibitory activity[39].

Experimental evidence involving *in vivo* trials has also exhibited positive results. During a 12 week feeding trial on 30 spontaneously hypertensive rats (SHR), a reduction of 17 mm Hg in systolic blood pressure (SBP) was reported upon consumption of sour milk containing 2.5-3.5 mg/kg/day of Val-Pro-Pro and Ile-Pro-Pro fermented by *L. helveticus* LBK-16H (10%)[40] . In another study, Hata *et al.* (1996) used a single-blind, placebo-controlled study involving 30 elderly hypertensive patients. The authors reported that ingestion of 95 ml of sour milk fermented with *L. helveticus* and *Saccharomyces cerevisiae* per day for eight weeks had significantly decreased SBP and diastolic blood pressure (DBP) by 14.1 mm Hg and 6.9 mm Hg, respectively[41]. In one of the largest studies, involving 94 hypertensive subjects in a double-blind, placebo-controlled, randomized trial, Jauhiainen *et al.* found that the consumption of 150 mL milk fermented by *L. helveticus* twice a day for 10 weeks could decrease SBP and DBP by 4.1 mm Hg and 1.8 mm Hg, respectively[42].

Future Perspectives

Bacteriocins and the organisms that produce them have potential in the food and feed industry as a source of probiotics, as well as in the pharmaceutical industry as a source of probiotics. Bacteriocins are also useful in food and feed industry because of their antibacterial characteristics; moreover, bacteriocins can be used as bio preservatives in fermented foods[43]. As lactic acid bacteria tend to produce baceriocins and as they are capable of inhibiting gram positive and a majority of gram negative bacteria, in the future such bacteriocins may be as such used as bio preservatives in fermented and salt rich vegetable and fruit products. Particularly, in sauerkrauts and pickles these may be used and salt ($NaCl_2$) and other preservatives containing Na~~Cl_2~~ may be reduced, thereby even the hypertensives may enjoy these foods without much their blood pressure getting affected. However, the usage of such bacteriocins should be prudent as all the bacteriocins are not the same and may be toxic if produced by other pathogens.

CONCLUSION

This review has illustrated the possible benefits of probiotics in mediating hypertension by means of various positive modulations of diverse physiological systems. Considering the magnitude of the health and financial consequences of HTN, scientific search for more effective and at the same time most affordable means of tackling HTN has become more than a necessity. Probiotics could serve as a complementary supplement to enhance the well-being for those already suffering the diseases and taking drugs or hormonal therapy to medicate the condition. Further revelation on the potential of probiotics in future research could lead to a boost in probiotic-fermented food industries– dairy and non–dairy. Furthermore, formulation of novel foods containing both prebiotics and probiotics would serve as convenient foods offering a synergetic effect. However, more studies are needed to explore the exact *in vivo* mechanisms, shelf life & safety, prior to consider probiotics as an antihypertensive alternative treatment.

REFERENCES

1. FAO/WHO. Guidelines for the evaluation of probiotics in food. London Ontario Canada April 30 and May 1 2002.
2. Huey-Shi Lye, Chiu-Yin Kuan, Joo-Ann Ewe, Wai-Yee Fung and Min-Tze Liong "The Improvement of Hypertension by Probiotics: Effects on Cholesterol, Diabetes, Renin, and Phytoestrogens" Int. J. Mol. Sci. 2009, 10, 3755-3775.
3. Ostchega, Y., Yoon, S. S, Hughes, J., & Louis, T. (2008). Hypertension awareness, treatment, and control – continued disparities in adults: United States, 2005-2006. NCHS Data Brief, (3), 1-8.
4. American heart association web site.Understanding blood pressure readings. 2011. http:www.heart.org/HEARTORG/conditions/High blood pressure/ about blood pressure/UCM_301764_article.jsp.
5. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–23.
6. Deepa R, Shanthirani CS, Pradeepa R, Mohan V. Is the 'rule of halves' in hypertension still valid?--Evidence from the Chennai Urban Population Study. J Assoc Physicians India 2003; 51 : 153-7.
7. INTERSALT Co-operative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT study. J Hypertens.1988;6(Suppl 4):S584–6.
8. Sever PS, Poulter NR. A hypothesis for the pathogenesis of essential hypertension:the initiating factors. J Hypertens. 1989;7(Suppl 1):S9–12.
9. Whelton PK, He J, Appel LJ, *et al*., Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program, JAMA, 288, 2002, 1882-1888.
10. Appel LJ, Moore TJ, Obarzanek E, *et al*., A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group, N. Engl. J. Med., 336, 1997, 1117-1124.
11. Ascherio A, Hennekens C, Willett WC, *et al*., Prospective study of nutritional factors, blood pressure, and hypertension among US women, Hypertension, 27, 1996, 1065- 1072.
12. Lairon D, Arnault N, Bertrais S,*et al*., Dietary fiber intake and risk factors for cardiovascular disease in French adults, Am. J. Clini. Nutri., 82, 2005, 1185- 1194.
13. Miura K, Greenland P, Stamler J, Liu K, Daviglus ML and Nakagawa H, Relation of vegetable, fruit, and meat intake to 7-year blood pressure change in middle-aged men: the Chicago Western Electric Study, Am. J. Epidemiol., 159, 2004, 572-580.
14. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T and Trichopoulou A: Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek
15. European Prospective Investigation into Cancer and Nutrition (EPIC) study, Am. J. Clini. Nutri., 80, 2004, 1012- 1018.
16. Sacks FM, Svetkey LP, Vollmer WM, et al., Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet, DASH Sodium Collaborative Research Group, N. Engl. J. Med., 344, 2001, 3- 10.
17. Srinath Reddy K and Katan MB, Diet, nutrition and the prevention of hypertension and cardiovascular diseases, Public Health Nutri., 7, 2004, 167-186.
18. Svetkey LP, Simons-Morton D, Vollmer WM, et al., Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial, Arch. Int. Med., 159, 1999, 285- 293.
19. Stamler J, Liu K, Ruth KJ, Pryer J and Greenland P: Eight-year blood pressure change in middle aged men: relationship to multiple nutrients, Hypertension, 39, 2002, 1000-1006.
20. Ascherio A, Rimm EB, Giovannucci EL, et al., A prospective study of nutritional factors and hypertension among US men, Circulation, 86, 1992, 1475-1484.
21. Kuppasani K, Reddi AS. Emergency or urgency? Effective management of hypertensive crises. JAAPA. 2010;23:44–49.
22. Smithburger PL, Kane-Gill SL, Nestor BL, Seybert AL. Recent advances in the treatment of hypertensive emergencies. Crit Care Nurse. 2010;30(5):24–30. quiz 31.
23. Varon J. Treatment of acute severe hypertension: current and newer agents. Drugs. 2008;68(3):283–297
24. Varon J, Marik PE. Clinical review: the management of hypertensive crises. Crit Care. 2003;7(5):374–384.
25. Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. Vasc Health Risk Manag.2010;6:457–464.
26. Ahuja K, Charap MH. Management of perioperative hypertensive urgencies with parenteral medications. J Hosp Med. 2010;5(2):E11–E16.
27. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet. 2000;356(9227):411–417.
28. Polly DM, Paciullo CA, Hatfield CJ. Management of hypertensive emergency and urgency. Adv Emerg Nurs J. 2011;33(2):127–136
29. Belsha CW. Management of hypertensive emergencies. In: Jtfe AL, editor. Clinical Hypertension and Vascular Diseases: Pediatric Hypertension. Berlin, Germany: Springer Science+Business Media; 2011. pp. 559–574.
30. Kessler CS, Joudeh Y. Evaluation and treatment of severe asymptomatic hypertension. Am Fam Physician. 2010;81(4):470–476.
31. FitzGerald RJ, Murray BA, Walsh DJ. Hypotensive peptides from milk proteins. J. Nutr.2004;134:980S–988S.
32. Inagami T. The renin-angiotensin system. Essays Biochem. 1992;28:147–164.
33. Saito T. In: Advances in Experimental Medicine and Biology: Bioactive Components of Milk.Bösze Z, editor. Springer; New York, NY, USA: 2008.
34. Korhonen H. Milk-derived bioactive peptides: From science to applications. J. Func. Foods.2009;1:177–187.
35. Yamamoto N, Takano T. Antihypertensive peptides derived from milk proteins. Nahrung.1999;43:159–164.

36. Donkor ON, Henriksson A, Vasiljevic T, Shah NP. *α*-Galactosidase and proteolytic activities of selected probiotic and dairy cultures in fermented soymilk. Food Chem. 2007;104:10–20.
37. Rhyänen EL, Pihlanto-Leppälä A, Pahkala E. A new type of ripened: Low-fat cheese with bioactive properties. Int. Diary J. 2001;11:441–447.
38. Ng KH, Lye HS, Easa AM, Liong MT. Growth characteristics and bioactivity of probiotics in tofu-based medium during storage. Ann. Microbiol. 2008;58:477–487
39. Fung WY, Woo YP, Liong MT. Optimization of growth of *Lactobacillus acidophilus* FTCC 0291 and evaluation of growth characteristics in soy whey medium: A response surface methodology approach. J. Agr. Food Chem. 2008;56:7910–7918.
40. Sipola M, Finckenberg P, Santisteban J, Korpela R, Vapaatalo H, Nurminen ML. Long-term intake of milk peptides attenuates development of hypertension in spontaneously hypertensive rats. J. Physiol. Pharmacol. 2001;52:745–754.
41. Hata Y, Yamamoto M, Ohni M, Nakajima K, Nakamura Y, Takano T. A placebo-controlled study of the effect of sour milk on blood pressure in hypertensive subjects. Am. J. Clin. Nutr.1996;64:767–771
42. Jauhiainen T, Collin M, Narva M, Poussa T, Korpela R. Effect of long-term intake of milk peptides and minerals on blood pressure and arterial function in spontaneously hypertensive rats. Milchwissenschaft. 2005;60:358–362
43. Raja Narender.B, , Ravi.P, , A. Shyam Sunder, And V. Mallikarjun. Isolation and Characterization of Bacteriocins From Fermented Foods and Probiotics. International Journal of Pharma and Bio Sciences, Vol.1/Issue-3/Jul-Sep.2010