Pharmacological Research 153 (2020) 104663

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Effect of *Lactobacillusplantarum* containing probiotics on blood pressure: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Probiotic
Lactobacillus plantarum
Blood pressure
Hemodynamic parameters
Meta-analysis

ABSTRACT

Previous studies have recommended that probiotics may have blood pressure (BP)-lowering effects. However, they examined all probiotic strains (multi/single probiotics) simultaneously. In respect to strain specificity properties of probiotic, the aim of the present study was to systematically investigate the role of *Lactobacillus plantarum* as an anti-hypertensive agent by performing a meta-analysis of randomized controlled trials. PubMed, Scopus, Cochrane Library and Google Scholar were used from inception until October 2018 to identify eligible trials. We used random-effects model as the preferable method to assess the combined treatment effect. We further conducted sensitivity analysis and stratified analysis. Seven studies with 653 participants were included in the meta-analysis. The pooled weighted mean difference (WMD) with the random effects model showed a significant effects of *Lactobacillus plantarum* supplementation on improvement of SBP with no statistically significant heterogeneity (WMD: -1.58 mmHg, 95 % CI: -3.05 to 0.11) (heterogeneity P = 0.14; I^2 = 36 %). The overall effect in the DBP showed significant pooled estimates (WMD: -0.92 mmHg, 95 % CI: -1.49 to -0.35) with a complete homogeneity between the studies (heterogeneity P = 0.46; I^2 = 0 %). The findings of the present meta-analysis study support the use of *Lactobacillus plantarum* supplementation for lowering systolic and diastolic blood pressure. The clinical significance of blood pressure-lowering effect of *Lactobacillus Plantarum* supplementation is not considerable; however, given the overarching benefits evident and concurrent lack of specific side effects, further trials are warranted to clarify the effects of *Lactobacillus Plantarum* probiotics particularly for hypertensive patients.

1. Introduction

Hypertension (HTN) is one of the major risk factors of cardiovascular disease worldwide [1–3], with an extensive prevalence reaching over one billion people all over the world [4]. In recent years, the use of nutritional therapy in the management of HTN has been given much attention [5]. Several nutraceuticals have shown to enhance the efficacy of classic pharmacological treatments. An improvement in the quality of the treatment such as adherence to therapy and achieving clinically optimal blood pressure is associated with the use of blood pressure-lowering nutraceuticals [6]. Therapeutic diets such as DASH (Dietary Approaches to Stop Hypertension) along with the use of numerous herbal compounds (e.g., turmeric, cinnamon, and ginger) have shown positive and significant impacts on HTN as well as inflammatory conditions in humans [7,8].

One of the highlighted therapeutic approaches is probiotic supplements that have emerged as a new therapeutic option in the treatment of cardiovascular diseases. Recently, several studies have suggested that the use of probiotics is associated with significant effects on a wide range of diseases including HTN, atherosclerosis, inflammatory and cardiovascular diseases [9]. *Lactobacillus plantarum* is one of the most important probiotics that is employed as a nutritional supplement. It has been observed that this genus has some effects on metabolic disorders and cardiovascular diseases [10,11]. A number of clinical trials have been conducted to evaluate the effect of *Lactobacillus plantarum* on HTN [12]. However, the results of these studies were inconsistent; In the Hariri's study, supplementation with *Lactobacillus plantarum* showed a significant reduction in HTN, while in another study by Sharafedtinov, the use of *Lactobacillus plantarum* had no significant effect on blood pressure subjects compared to the placebo group [12,13]. Several meta-analyses have also been published investigating the role of probiotics in hypertensive patients. These studies

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https://doi.org/10.1016/j.phrs.2020.104663
Received 12 June 2019; Received in revised form 5 January 2020; Accepted 23 January 2020
Available online 24 January 2020

revealed the positive effects of probiotic supplementation on lowering blood pressure [14–17]. Given that the effects of each probiotic are specific (Strain-Specificity), and a particular strain may show different effects on blood pressure, it is recommended to examine each strain separately. There has not been a comprehensive meta-analytical study on the effect of *Lactobacillus plantarum* supplementation on blood pressure; thus, we conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) on the role of *Lactobacillus plantarum* including all sub-strains as an anti-hypertensive, as to our knowledge, this topic has not been assessed previously.

2. Materials and methods

We conducted our systematic review and meta-analysis based on the recommendations and guidelines reported in PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) [18,19].

2.1. Literature search

Two independent researchers searched several databases including PubMed, Scopus, Cochrane Library and Google Scholar from inception until October 2018. Terms used for the search included [Lactobacillus plantarum OR L. plantarum AND hypertension OR high blood pressure OR SBP OR DBP] in an attempt to find all related clinical trials investigating the effects of *Lactobacillus plantarum* on high blood pressure. We also hand searched the reference lists of eligible studies. Any disagreement between the two researchers was discussed and resolved by a third researcher.

2.2. Study selection

Studies were considered for inclusion in our systematic review if they fulfill the following inclusion criteria [1] examined the effects of *Lactobacillus plantarum* on blood pressure as the primary or secondary outcome [2], *Lactobacillus plantarum* (including all sub-strains) was administered as either single strain or multi-strain supplement [3], randomized, placebo-controlled trials [4], reported either the mean (or net change of) systolic and/or diastolic blood pressure and associated standard deviation (SD) or the necessary values for calculating the parameters. We excluded cohort or cross-sectional studies, reports that did not include control group or placebo, as well as animal studies. All studies were screened independently by two researchers and any conflict discussed by the third researcher to determine the final outcome. Fig. 1 shows the process of inclusion of studies in the systematic review.

2.3. Data extraction

Two sections of data were extracted from the included articles: basic and main characteristics. Basic characteristics comprised name of the author, year of publication, country where the trial was conducted, design of the study (parallel, cross-over, etc.), age and sex of the subjects, duration of the study, supplementation dosage, clinical condition and initial systolic and diastolic blood pressure measurements of the intervention group. With respect to the main characteristics, mean systolic and diastolic blood pressure (SBP/DBP) in intervention and control groups with their standard deviations (SD) and the number of subjects in the intervention and placebo groups were extracted from the main text, tables, figures or supplementary data. In the case of missing data, we contacted corresponding authors for missing data.

2.4. Quality assessment

A systematic assessment of bias was conducted using Jadad scale [20]. We evaluated the included RCTs for [1] statement of randomization and method of random allocation [2]; use of blinding and method applied [3]; detail of withdrawals/dropouts. Both of the randomization and blinding sections have a maximum of 2 points, and the dropouts section can earn 1 point. The minimum score which can be earned for each article is 0 and its maximum is 5. Articles with score of < 3 were considered as low-quality articles and those with a score of ≥ 3 were considered as high-quality ones [20].

2.5. Statistical analysis

For the statistical analyses, we used Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, England) and Comprehensive Meta-Analysis (version 3.2; Biostat). In order to assess the effects of *Lactobacillus plantarum* on blood pressure, we used the weighted mean difference (WMD) and its 95 % confidence interval. Following Cochrane, we used mean and SD values for blood pressure (SBP/DBP) before and after using the supplements in both intervention and placebo groups to calculate the effect size [21]. According to Hozo et al., all studies' median values and their ranges or their confidence intervals (CI) were converted to mean and SD [22]. Heterogeneity between studies was evaluated by the Cochran's Q-test at $P < 0.05$ level of significance and I^2 test. A random-effects model was employed in the meta-analysis. We carried out subgroups analysis to investigate potential sources of heterogeneity which we expected to include: duration of study (≤ 7 weeks and > 7 weeks), blood pressure in subjects (normal, elevated and hypertension) and the content of supplements used in intervention (*Lactobacillus plantarum* supplements or multi-strain supplements that contained *Lactobacillus plantarum*). We also carried out sensitivity analyses to assess the effect of each trial on the pooled estimate. We applied Begg's funnel plot to determine publication bias [23]. Begg's rank correlation test and Egger's regression test were used to infix funnel plot incommensurability [24].

3. Results

3.1. Search results and study eligibility

Fig. 1 shows the process of study selection. A total of 1642 papers were retrieved primarily from the electronic searches. Two of the authors reviewed the title and abstracts of the papers at a later step and duplicates and studies that were not related to *Lactobacillus plantarum* and blood pressure were removed. In the next step, the full texts of the remaining articles were read. Two studies were excluded due to lack of a placebo group, 3 studies were not written in English, one study was also excluded due to lack of appropriate study design and another for the low-quality score based on the Jadad scale. Finally, seven studies were included in our systematic review and meta-analysis.

3.2. Description of the studies

The included clinical trials were published between 2002 and 2017 in South Korea [25], Iran [13], Estonia [26], the United States [27], Poland [28], Russia [12] and Sweden [29]. Four studies were double-blinded, randomized, placebo-controlled trials [13,25,27,28] and three were designed as a parallel study [12,26,29]. In the study of Sharafedtinov et al., systolic and diastolic blood pressure were measured in the morning and evening, but for the analysis, we used only the blood pressure of the morning [12]. Two interventions have been carried out in the Xu et al. study, which was designed as a parallel design; but given that results might have been affected by the potential antihypertensive effect of the intake of blueberries, which are fermented by *Lactobacillus plantarum*, we did not analyze this intervention [29]. A total of 653 subjects were analyzed in this study, 337 subjects were in the intervention group and 316 subjects were in the placebo group. All of the participants in the studies were both males and females who had different clinical conditions including hypertension [29], hypertriglyceridemia [25], obesity [12], type 2 diabetes mellitus [13] and smoking [28]. The duration of trials varied from 2 to 12 weeks. Baseline systolic

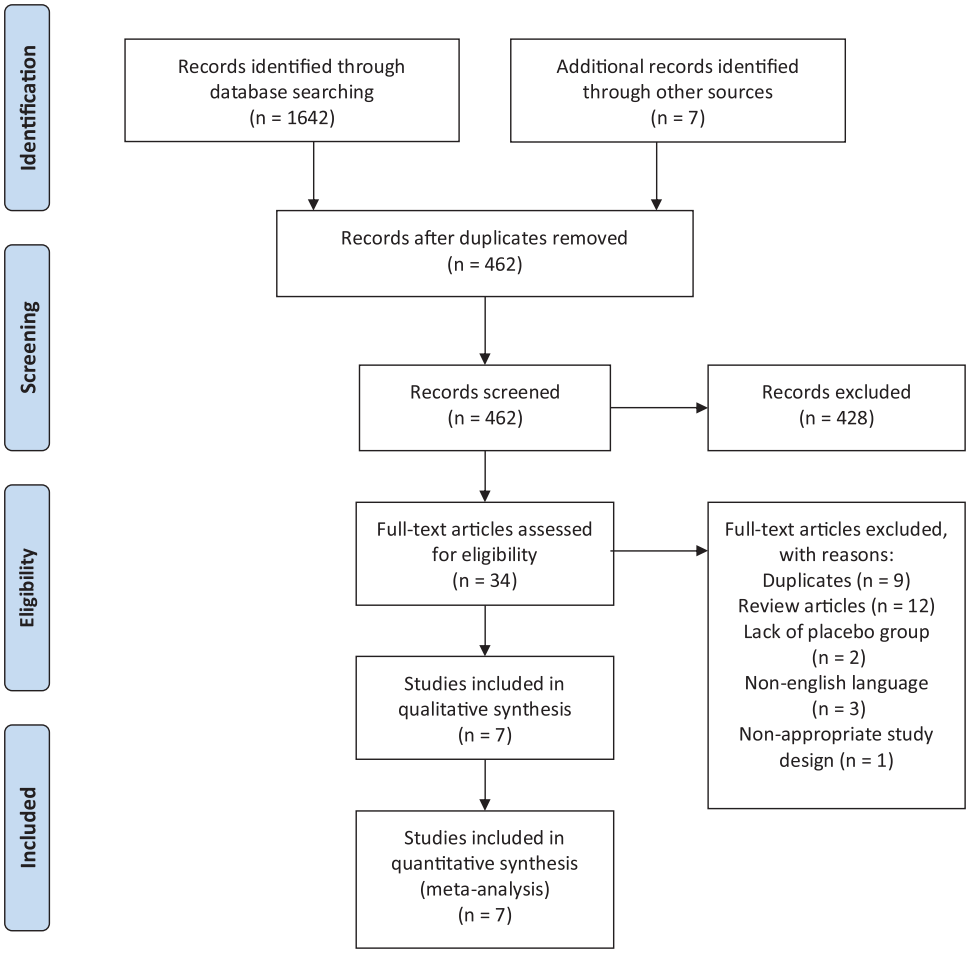


Fig. 1. Flow diagram of study selection.

blood pressure (SBP) ranged from 115.08 mmHg to 151.5 mmHg in the intervention group. The baseline diastolic blood pressure (DBP) in the intervention group ranged from 68.44 mmHg to 100 mmHg. All included trials reported both systolic and diastolic blood pressures before and after the intervention [12,13,25–29]. The lowest daily dose of *Lactobacillus plantarum* was 10^9 cfu of *Lactobacillus plantarum DSM* 15313 which was administered in Xu study [29] and the highest dose was used in Sharafedtinov's study with 1.5×10^{12} cfu/day of *Lactobacillus plantarum TENSIA* [12]. Regarding the intervention groups, two studies used probiotic dairy products [12,26], 3 trials used probiotic drinks [13,28,29] and one study used probiotic capsules as supplementation in the intervention group [27]. The treatments in control groups of included studies were: Multi-component powder [25], soy milk [13] capsule filled with 0.6 g of cornstarch [27], Multi-component structure including rosehip powder [28], probiotic-free cheese [12], and probiotic-free placebo drink [29]. Five studies used *Lactobacillus plantarum* as the probiotic supplementation [12,13,26,28,29] and 2 studies have used multi-strain probiotics supplement in addition to *Lactobacillus plantarum* as the intervention [25,27]. There were no serious reported side effects of *Lactobacillus plantarum* on individuals in all of the included RCTs [12,13,25–29]. Table 1 shows the characteristics of the included clinical trials.

3.3. Jadad score assessment

Based on the assessment conducted by two independent researchers, all the articles included in our systematic review were high quality according to the Jadad scale. Table 2 shows the details of the Jadad scoring of the clinical trials. The trials of Ahn, Sharafedtinov and Xu received only one point of the blinding score as they have just mentioned that blinding was carried out [12,25,29]; however, the rest of the studies received the highest score regarding this section [13,26–28]. Regarding randomization, only one study took one point for not referring to the random allocation method [26,28]. The remaining studies were fully scored based on randomization [12,13,25,27,29]. All papers scored one point due to stating the dropouts and participant withdrawals [12,13,25,27,29], except for Hütt and Naruszewicz which did not mention the fate of participants [26,28]. Finally, with respect to the overall score that reflects the quality of the articles included, all papers received a score of ≥ 3, which indicates that all included trials are of high quality [12,13,25–29].

3.4. Pooled effect size of Lactobacillus plantarum supplementation on blood pressure

The pooled weighted mean difference (WMD) with the random effects model showed a significant effects on improvement of SBP with a non-significant heterogeneity after supplementation with *Lactobacillus plantarum* (WMD: -1.58 mmHg, 95 % CI: -3.05 to -0.11, $P < 0.05$) (test for heterogeneity $P = 0.14$; $I^2 = 36$ %). In respect to DBP, the overall effect in the DBP showed significant pooled estimates (WMD: -0.92 mmHg, 95 % CI: -1.49 to -0.35) and there was complete homogeneity between the studies (test for heterogeneity $P = 0.46$; $I^2 = 0$ %) (Fig. 2).

3.5. Subgroup analysis

Subgroup analysis was performed to identify potential sources of heterogeneity and was based on a number of variables including: the

Table 1
Characteristics of included trials.

Author	Year	Design of studies	Country	No. of Subjects in case group	No. of controls	Gender	Age (mean)	Follow-up Duration	Clinical Condition	Dosage (daily)	Significant Outcome	Baseline BP
Ahn	2015	Randomized, double-blind, placebo-controlled trial	South Korea	46	46	M F	54.1	12 weeks	Nondiabetic and hypertriglyceridemic subjects	2 g of powder containing 5×10^9 cfu of L. curvatus HY7601 and 5×10^9 cfu of L. plantarum KY1032	Individuals in the probiotic group exhibited a 20 % reduction in their serum TG levels and a significant 25 % increase in their plasma apo A–V levels.	120.4 /78.3
Hariri	2014	Randomized, double-blind, controlled clinical trial	Iran	20	20	M F	56.9	8 weeks	Type 2 diabetes mellitus	200 ml of probiotic soy milk containing 2×10^9 cfu of L. plantarum A7	Probiotic soymilk significantly decreased systolic and diastolic BP.	147/100
Hütt C (Cheese trial)	2015	Two double-blinded randomized placebo-controlled exploratory trials	Estonia	82	82	M F	37.7	3 weeks	Healthy adults	50 g of probiotic cheese containing 10^{10} cfu of L. plantarum TENSIA	Both systolic and diastolic baseline BP values of participants in the cheese and yoghurt trials differed significantly.	131/83.4
Hütt Y (Yoghurt trial)	2015	Two double-blinded randomized placebo-controlled exploratory trials	Estonia	43	43	M F	34.2	3 weeks	Healthy adults	150 g of probiotic yoghurt containing 6×10^9 cfu of L. plantarum TENSIA	Both systolic and diastolic baseline BP values of participants in the cheese and yoghurt trials differed significantly.	118.9/76.7
Möller	2017	Double-blind, randomized, placebo-controlled trial	USA	57	48	M F	19.8	2 weeks	Young adults	One probiotic capsule containing 11.25×10^{10} cfu of Bifidobacterium breve, B.longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, and Streptococcus thermophilus	Compared to placebo, two-week probiotic supplementation did not affect resting measures of cardiovascular function, cardiovascular responses during or recovery from stress, or psychological reactions to acute psychological stress.	115.08/ 68.44
Naruszewicz	2002	Controlled, randomized, double-blind trial	Poland	18	18	M F	42.3	6 weeks	Smokers	400 ml of the test product containing 5×10^7 of L. plantarum 299v	Significant decreases in systolic blood pressure, leptin, and fibrinogen were recorded in the experimental group. Decreases in F2-isoprostanes and interleukin-6 were also noted in the experimental group in comparison with baseline.	134/89
Sharafedtinov	2013	Randomized, double-blind, placebo-controlled, parallel pilot study	Russia	25	15	M F	52	3 weeks	Obese hypertensive patients	50 g of probiotic cheese containing 1.5×10^{11} cfu of L. plantarum TENSIA	Body mass index (BMI) was significantly reduced in the probiotic cheese group versus the control cheese group. In patients simultaneously treated with BP-lowering drugs, similar reductions of BP were observed in both groups.	134/82.4
Xu	2015	Double blind, randomized Placebo-controlled trial	Sweden	46	44	M F	65	12 weeks	Hypertension	125 ml of the fruit drink mixed with probiotic powder containing 10^9 cfu of L. plantarum DSM 15313	After 3 months there was a significant difference in the change of the DBP between groups BL and L.	151.5/93.4

Table 2
Quality of the included studies based on the Jadad score.

Study; Year	Blinding	Randomization	Withdrawals and dropouts descriptions	Score
Ahn; 2015	1	2	1	4
Hariri; 2014	2	2	1	5
Hütt; 2015	2	1	0	3
Möller; 2017	2	2	1	5
Naruszewicz; 2002	2	1	0	3
Sharafedtinov; 2013	2	2	1	5
Xu; 2015	1	2	1	4

study duration, baseline blood pressure, and the composition of supplements given (Table 3). Our findings indicated that SBP and DBP are not associated with significant changes after subgroup analysis based on the duration of supplementation. In other subgroup analysis based on baseline blood pressure of subjects, individuals with hypertension revealed a significant reduction in diastolic blood pressure with a non-significant heterogeneity after supplementation with *Lactobacillus plantarum* (WMD; -1.11 mmHg and its CI; -1.94 to -0.27). In the third subgroup analysis which was based on the supplements components, single strain supplements of *Lactobacillus plantarum* showed a significant reduction on both SBP (WMD; -1.81 and its CI; -3.59 to -0.02, P = 0.05, I2 = 50 %) and DBP level (WMD; -1.02 and its CI; -1.64 to -0.41, P = 0.001, I2 = 0.0 %), while the meta-analysis of the multi-strain supplements did not show any significant improvement of DBP in favor of probiotic supplementation.

3.6. Sensitivity analysis

We executed a leave-one-out sensitivity analysis to explore the effect of single studies on the overall effect size. The pooled estimate of mean difference of SBP and DBP ranged from -1.31 (95 % CI = -2.24, -0.38) to -2.06 (95 % CI = -4.15, 0.02) in SBP and -0.53 (95 % CI = -1.20, 0.13) to -1.51 (95 % CI = -2.39, -0.63) in DBP (Fig. 3).

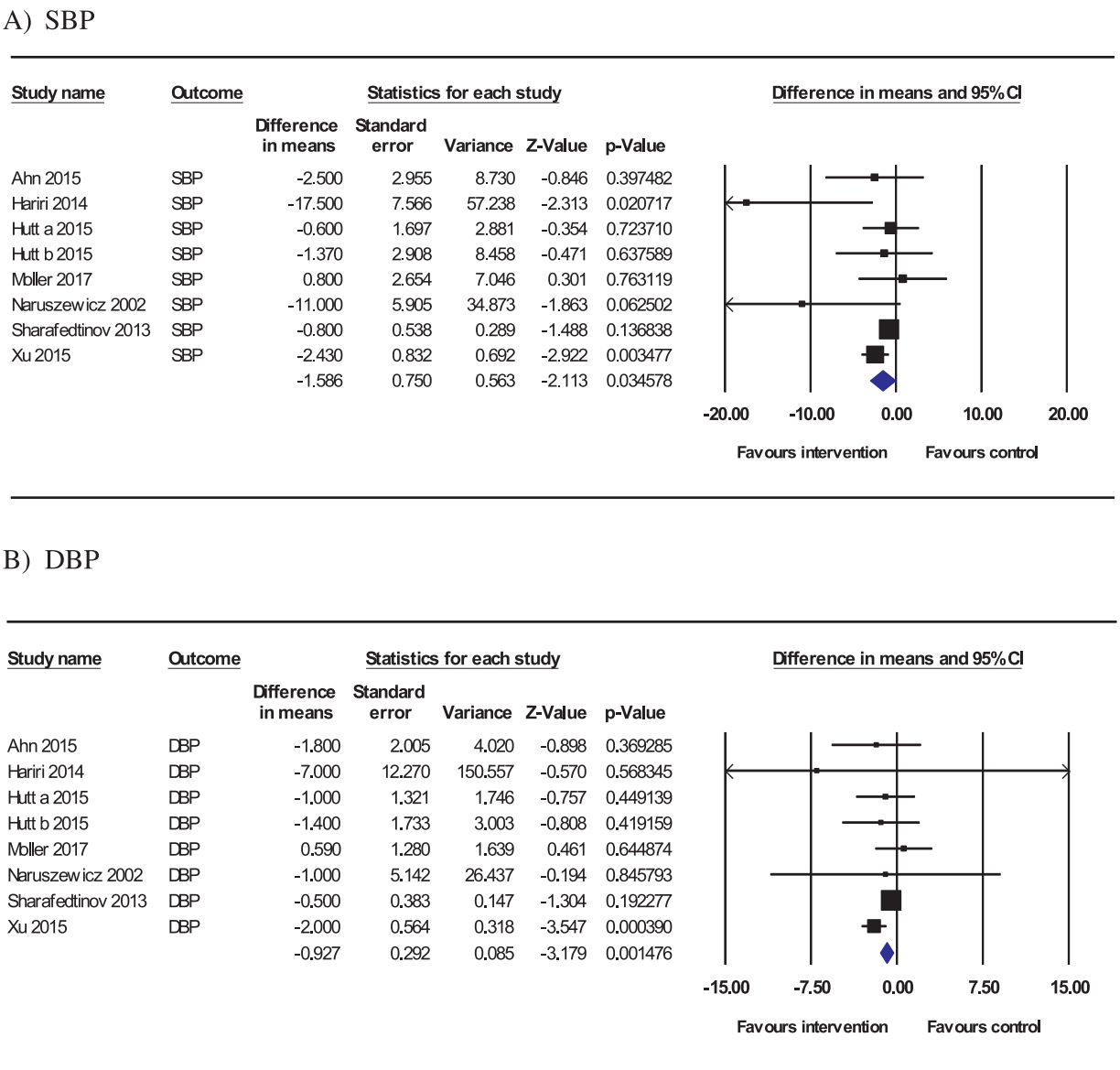


Fig. 2. Meta-analysis of the effects of *Lactobacillus plantarum* on A) SBP and B) DBP. Weight of studies was assigned by Review manager (Version 5.03) using the sample size and SD. Sizes of data markers reveal the weight of each trial. The diamond represents the overall pooled effect size. Random effects model was used to pool the standard mean differences of indicators. CI, confidence interval; I-squared inconsistency. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3
: Subgroup analysis[a].

subgroup			WMD (95 % CI)	Test for overall effect	Test for heterogeneity	I2(%)
Duration of study, weeks						
	≤7 weeks					
		SBP	−0.82 [-1.82, 0.18]	P = 0.11	P = 0.49	0
		DBP	−0.49 [-1.20, 0.22]	P = 0.17	P = 0.88	0
	> 7 weeks					
		SBP	−3.65 [-8.12, 0.81]	P = 0.11	P = 0.14	49
		DBP	−0.49 [-1.20, 0.22]	P = 0.17	P = 0.88	0
Blood pressure stage, mm Hg						
	Normal					
		SBP	−0.18 [-4.02, 3.65]	P = 0.93	P = 0.58	0
		DBP	−0.10 [-2.10, 1.90]	P = 0.92	P = 0.35	0
	Elevated					
		SBP	−2.50 [-8.29, 3.29] −	P = 0.40	Not applicable	Not applicable
		DBP	1.80 [-5.67, 2.07]	P = 0.37	Not applicable	Not applicable
	Hypertension	***SBP***	−1.92 [-3.95, 0.10] −	P = 0.06	P = 0.04	60
		DBP	1.11 [-1.94, -0.27]	P = 0.010	P = 0.30	19
Supplement compounds	Lactobacillus plantarum	***SBP***	−1.81 [-3.59, -0.02]	P = 0.05	P = 0.07	50
	Multi-strain probiotic	***DBP***	-1.02 [-1.64, -0.41]	P = 0.001	P = 0.42	0
		SBP	−0.67 [-4.53, 3.19]	P = 0.73	P = 0.41	0
		DBP		P = 0.93	P = 0.31	2

[a] Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMD, weighted mean difference; CI, confidence interval; I2, percentage score for heterogeneity.

3.7. Publication bias assessment

No publication bias was identified according to the visual inspection of funnel plots symmetry. Although, The Begg's rank correlation test of SBP revealed a slight publication bias (Kendall's Tau with continuity correction: -0.60; z = 2.10; two-tailed p = 0.03), other supplemental methods including Begg's rank correlation test of DBP (Kendall's Tau with continuity correction:-0.32; z = 1.11; two-tailed p = 0.26), Egger's linear regression test of SBP (intercept: -0.94; standard error: 0.60; 95 % CI: -2.41, 0.52; t = 1.57, df = 6; two-tailed p = 0.16); DBP: (intercept:-0.24; standard error: 0.55; 95 % CI: -1.61, 1.11; t = 0.44, df = 6; two-tailed p = 0.67)] verified the lack of publication bias for the comparison of SBP and DBP levels between probiotic supplemented groups and placebo groups (Fig. 4).

4. Discussion

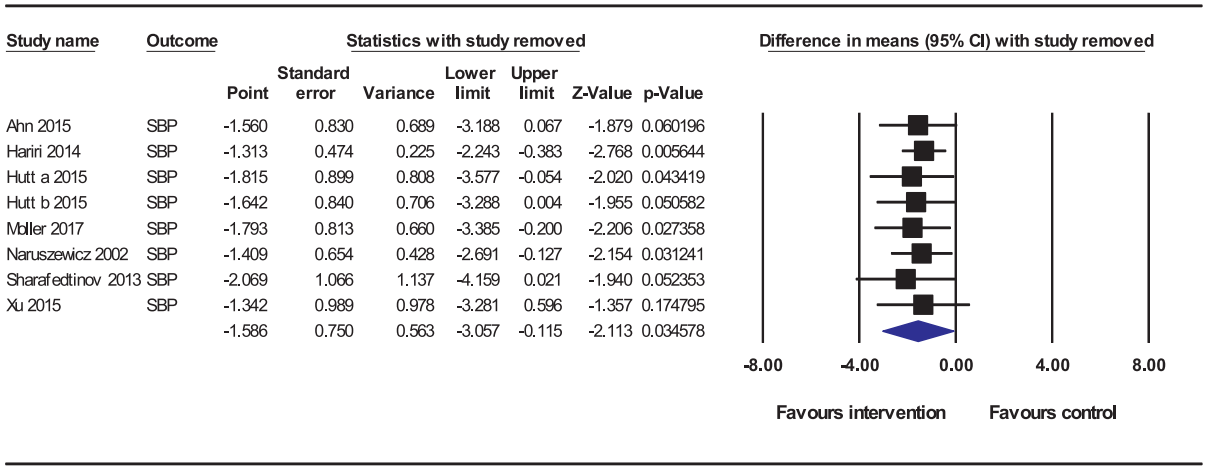
To our knowledge, this systematic review is the first to summarize the effect of *Lactobacillus Plantarum* probiotic supplementation on blood pressure. Based on our analysis of seven randomized clinical trials that assessed the role of this specific strain of probiotics on blood pressure, we have found a modest, yet significant decrease in SBP and DBP when pooling the results of included studies. Our results are to some extent similar to those reported by a previous meta-analysis that assessed the role of probiotics on blood pressure. However, some differences in our results need to be addressed. Primarily, the magnitude of the change in the BP was quite modest (reduction of SBP by 1.58 mmHg and DBP by 0.92 mmHg), even smaller than those reported by Khalesi et al. [15]. On the other hand, on conducting the subgroup analysis, we have found that single-supplementation with *Lactobacillus Plantarum* intake has a more pronounced effect on both systolic and diastolic BP in compared with multi-strain probiotics. Furthermore, this significant effect was only confined to those who had hypertension, not normotensives or patients with elevated blood pressure.

The difference in findings might be attributed to the confining our meta-analysis to one specific strain of probiotics which is *Lactobacillus Plantarum*. Worth highlighting are the results of the subgroup analysis, which showed that *Lactobacillus Plantarum* supplements intake exerted a significant reduction on both SBP and DBP levels, while the use of the multi-strain supplements did not show any significant reduction of blood pressure. Though we must stress that the numbers of the available randomized controlled studies addressing this topic are relatively small and the effect observed is not substantial, yet, it might draw the attention to this specific probiotic strain and a potential role in lowering blood pressure. If this finding is proved in further studies, *Lactobacillus Plantarum* might be a promising cheap adjuvant to antihypertensive medications. This should be further investigated in clinical trials as it is quite evident that the available literature lacks studies that measure the potential effect of probiotics if administered in conjunction with antihypertensive medications.

The mechanism of the potential antihypertensive effect of probiotics and its protective effect on endothelial function has not been fully understood but some recent studies have shown that high blood pressure might be associated with gut microbiota dysbiosis, which suggests that dietary interventions that correct gut microbiota, including probiotics, could be applied as a new therapeutic strategy for hypertension [30–32]. In a recent review by Robles-Vera et al. it has been demonstrated that gut microbiota can potentially influence host BP through multiple mechanisms including bacterial products that enter the circulation [30]. They have also reported that specific strains of probiotics, including Lactobacillus, can synthesize neurotransmitters, and that gut microbiota has important influences on host cell physiology through bacterial metabolic products such as short-chain fatty acids or trimethylamine-*N*-oxide or bacterial wall components such as lipopolysaccharide [30]. Another recent study published in Nature has reported that treatment with *Lactobacillus murinus* prevented salt-sensitive hypertension by modulating T_H17 cells, as the immune system has been found to be implicated in the development of hypertension, particularly interleukin-17A (IL-17A)-producing CD4+ T_H17 cells. The authors demonstrated that induction of T_H17 cells depends on gut microbiota as they connected high salt intake to the gut–immune axis and highlighted that gut microbiome could be a potential therapeutic target to counteract salt-sensitive conditions. They also demonstrated that diet-induced shifts in microbiome composition may have profound effects on the host, especially on T cells and that T_H17 cells are particularly affected by the abundance of specific commensal bacteria, and accordingly daily treatment with *L. murinus* led to a significant reduction in systolic blood pressure and normalization of diastolic blood pressure in animal models, and they corroborated their findings in humans by conducting an exploratory pilot study in healthy male volunteers.

More studies are needed to further assess the role of *Lactobacillus Plantarum* on hypertensive patients especially that this specific

A)



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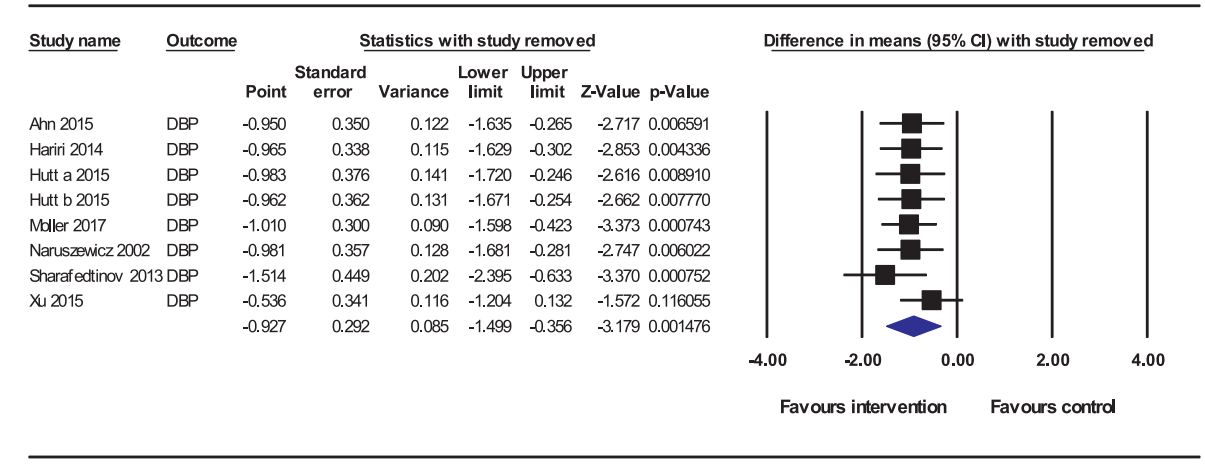


Fig. 3. Sensitivity analysis for the association between lactobacillus plantarum supplementation and (A) SBP and (B) DBP.

probiotic has been reported to act by different mechanisms including reduction of total cholesterol levels, γ-glutamyl transpeptidase, low-density lipoprotein, glucose, homocysteine and interleukin-6 that has been reported specifically in postmenopausal women [33]. All this might add to its benefits regarding the decrease of risk of cardiovascular disease among vulnerable populations.

4.1. Strengths and limitations

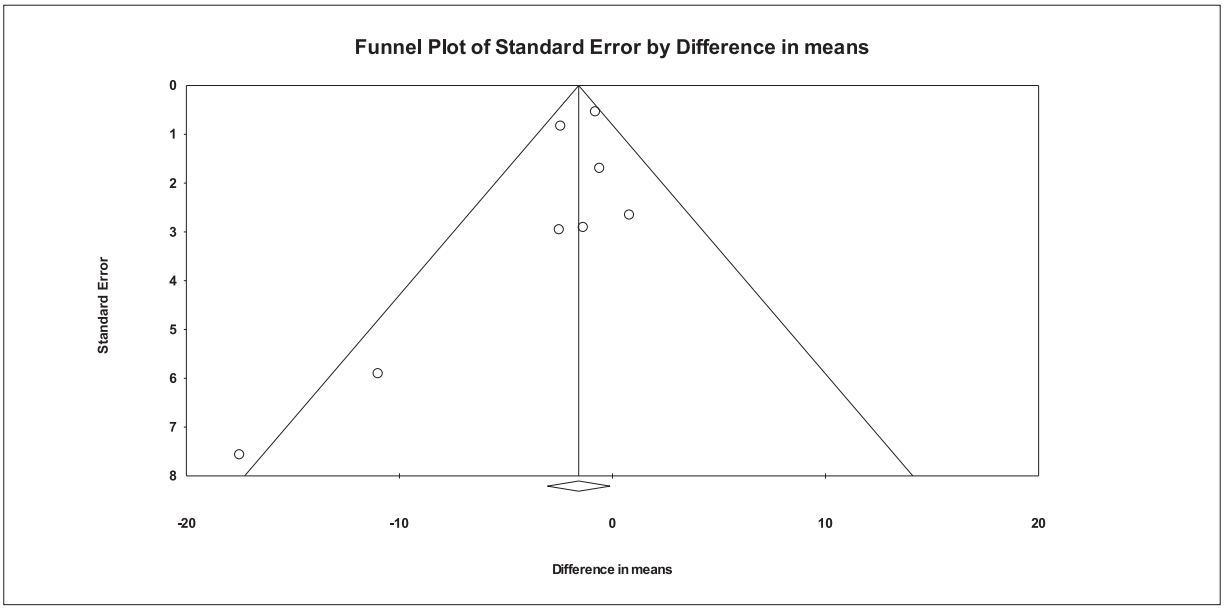
The main strength of this systematic review is our assessing the role of a specific species of probiotics, which has been recommended, given the diversity of probiotics and the different mechanisms by which they can act on the human body. This is specifically relevant when studying hypertension where a number of pathophysiological mechanisms are involved, in addition to the fact that the BP-lowering effects of specific probiotics are still unclear.

We also consider that we have carefully stratified the results by some relevant variables including the mode of administration of Lactobacillus and the baseline blood pressure status, which have shown that the antihypertensive effect of this specific probiotic strain is restricted to those with basal hypertension. The main limitation of our study is the relatively small number of retrieved studies, though it was expected given the specificity of the probiotic species chosen to be studied. Moreover, all sub-strains of *Lactobacillus Plantarum* were pooled in the analysis, whereas different sub-strains may exert variable results which should be considered as a potential limitation. Also, though meta-analyses have shown significant results, the strength of the retrieved potential association between *Lactobacillus Plantarum* administration and a lower systolic and diastolic blood pressure in hypertensive patients is weak and should be interpreted accordingly.

5. Conclusions

The findings of the present meta-analysis study support the use of *Lactobacillus plantarum* supplementation for lowering systolic and diastolic blood pressure. Additionally, unlike normal and elevated blood pressure subgroups, subjects with hypertension revealed a significant reduction in diastolic blood pressure. Furthermore, our work elucidated that single strain supplements of *Lactobacillus plantarum* may exert beneficial SBP and DBP-reducing effects in compared with the multi-strain supplements subgroup. The clinical significance of blood pressure-lowering effect of *Lactobacillus Plantarum* supplementation is not considerable; however, given the overarching benefits evident and concurrent lack of specific side effects, further trials are warranted to clarify the effects of *Lactobacillus Plantarum* probiotics particularly for hypertensive patients.

A)



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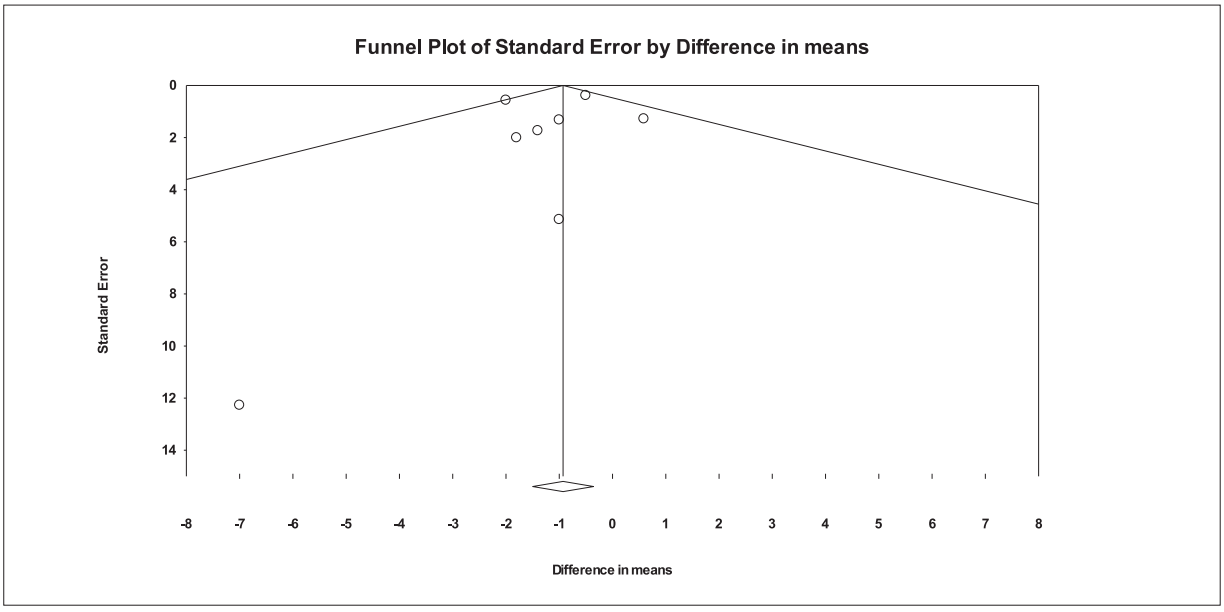

Fig. 4. Funnel plot displaying the publication bias in the included studies reporting the effect of lactobacillus plantarum supplementation on (A) systolic blood pressure and (B) diastolic blood pressure.

Declaration of Competing Interest

The authors declare no conflict of interest regarding the present article.

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