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Review Article

Could Probiotic Supplements Be an Effective Intervention to Reduce Hypertension? A Systematic Literature Review

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Abstract

Introduction: Pathogenesis of high blood pressure or hypertension is associated with microbial imbalance or dysbiosis of the gut microbiome. Previous research suggests probiotic consumption may reduce elevated blood pressure, possibly through manipulation of the gut microbiome, and may offer a future potential therapy for hypertension.

Aim: The aim of this research was to critically evaluate current research evidence to assess whether probiotic supplements may reduce high blood pressure and formulate recommendations regarding their use as an intervention to support hypertensive clients in a Nutritional Therapy context. The objectives were to outline the possible association between gut dysbiosis and hypertension, and to explore possible mechanisms by which probiotics may influence blood pressure.

Methods: A systematic review of the literature based upon PRISMA protocol was conducted. Four databases were searched: Cochrane Library (Central), CINAHL, Medline and TRIP from January 2014 until July 2020. Five eligible randomised controlled trials, including 453 participants, were identified and critically appraised to assess the quality of their evidence [1].

Results: Of the three highest quality studies, two supported probiotic supplements to be effective in reducing blood pressure, one study reported no effect. The remaining two studies were appraised to be of lesser methodological quality so were given less weighting for quality of evidence. This research study found moderate evidence that probiotic supplementation can significantly reduce blood pressure in individuals with borderline hypertension. No effect was reported in normotensives.

Conclusion: Probiotic supplementation may offer a convenient and effective adjunct for hypertensives to reduce high blood pressure alongside other dietary/lifestyle/medical interventions.

Recommendation: Further large-scale trials of longer duration on hypertensives are recommended to establish functional pathways, bacterial strain, dosage and required timescale.

Keywords: Probiotic Supplement; Hypertension; Dysbiosis; Blood Pressure; Gut microbiome

Abbreviations: ACE: Angiotensin-converting Enzyme; ACEI: ACE inhibitor; BASE: Bielefeld Academic Search Engine; BP: Blood pressure; CA: Critical appraisal; CINAHL: Cumulative Index of Nursing and Allied Health Literature; CONSORT: Consolidated Standards of Reporting of Trials; CFU: Colony Forming Units; CVD: Cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; DBP: Diastolic Blood Pressure; EC: Exclusion criteria; F/B: Firmicutes/Bacteroidetes; FMT: Faecal microbiota transplantation; GF: Germ free; GM: Gut microbiome; GPCR: G protein-coupled receptors; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; HBP: High Blood Pressure; HT: Hypertensive(s); HTN: Hypertension; IC: Inclusion criteria; ITT: Intention-to-treat; LR: Literature review; MA: Meta-analysis; MECIR: Methodological Expectations of Cochrane Intervention Reviews; MeSH: Medical Subject Heading; Met-S: Metabolic syndrome; mmHg: millimetres of Mercury; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NO: Nitric oxide; NS: Narrative synthesis; NT: Normotension/normotensive; Pre-HT: Pre-hypertensive; Pre-HTN: Pre-hypertension; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RAAS: Renin-Angiotensin-Aldosterone System; RCT: Randomised controlled trial; RO: Research objective; RoB: Risk of bias; RQ: Research question; SBP: Systolic Blood Pressure; SCFA: Short-chain fatty acid; SHR: Spontaneously hypertensive rat(s); SR: Systematic review; SNS: Sympathetic nervous system; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization

Introduction

Hypertension: High blood pressure (HBP) or hypertension (HTN) is a major cause of premature death with around 10.4 million deaths worldwide annually attributed to HTN [2] and around 75,000 deaths in England in 2015 [3]. Moreover, there are an estimated 1.13 billion hypertensives (HT) [4] and the Global Burden of Disease (2015) study recognises HTN as the second largest known global risk factor for disease after poor diet [5] presenting an important global health challenge. Defined as a systolic pressure ≥140mmHg and/or a diastolic pressure of ≥90mmHg on two different days [6], HTN is a recognised major risk factor for a number of pathophysiologies [2] including coronary heart disease, stroke and ischaemic heart disease as well as other complications such as renal impairment, visual impairment and peripheral vascular disease [4]. HTN in early adulthood increases an individual's risk of cardiovascular disease (CVD) [7]. An increase of 1.56 billion adults with HTN is forecasted by 2025 [8], with the growing burden of disease shifting to low income and developing countries [9], exacting a large public health burden on these countries.

Notwithstanding increased awareness, monitoring and a plethora of hypotensive pharmacotherapies, fewer than one in five people have their HTN under control and, with a global target to reduce its prevalence by 25% by 2025 [6], which is unlikely to be met [10], reduction of HTN presents a critical public health challenge. Collectively these statistics indicate a need for early intervention to prevent or ameliorate HTN.

Influences upon blood pressure: Influences upon BP are multifactorial and include lifestyle, environmental and genetic factors [11]. Targeted interventions to support healthy BP include eating plans such as the high-fibre, low-fat DASH (Dietary Approaches to Stop Hypertension) diet [12]. However, a significant focus has turned to the gut microbial population and their possible role in both BP maintenance and HTN development [13-15], with speculation that modification of the gut microbiota may offer novel therapeutic potential [16].

Gut microbiome: Although several hundred bacterial species reside in the gut, the predominant phyla, Firmicutes and Bacteroidetes compose over 90%, with a lower Firmicutes to Bacteroidetes (F/B) ratio generally considered a measure of good health [17]. Microbial diversity has been found to be inversely associated with increasing BP [18,19]. Moreover, an increase in the F/B ratio appears to correlate with increasing BP [20] implicating a disrupted gut microbial profile, known as dysbiosis, in HTN pathogenesis and suggests the GM may present a future area of focus in BP management.

Probiotics

Probiotics are defined by the Food and Agricultural Organization (FAO) of the United Nations and World Health Organization (WHO) as 'Live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host' [21], and are found naturally in foods such as yoghurt. Findings from a seminal systematic review (SR) and meta-analysis (MA) indicated an antihypertensive effect of probiotics [22,23]. Further evidence has accumulated in recent years to support beneficial effects of probiotics upon health, including HTN [24-26], although precise mechanisms remain unclear.

The overall aim of this research was to critically review more recent published studies to determine whether probiotics in supplement form may present a novel therapeutic tool to reduce HTN and, if so, formulate a probiotic supplement protocol to support hypertensive clients in a Nutritional Therapy setting. The research objectives were specifically

- To outline the possible association between gut dysbiosis and HTN from the existing evidence base.
- To explore possible mechanisms by which probiotics may influence blood pressure.
- To critically evaluate whether current research supports the use of probiotic supplements to manage HTN.
- To formulate recommendations as to the use of probiotic supplements as an intervention to support hypertensive clients in a Nutritional Therapy setting.

Methods

Study design

Placebo-controlled randomised controlled trials evaluating the effect of probiotic supplements on blood pressure were identified through a systematic literature review based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [27] and Methodological Expectations of Cochrane Intervention reviews (MECIR) [28].

Data collection

Predetermined search terms and inclusion/exclusion criteria were used to search for relevant journals in the databases below (Table 1). The search was conducted from January 2014 to ensure some overlap with [22] as the intention of this study was to look at emerging evidence since this seminal SR. Final search were carried out up to July 2020 resulting in a total of 1075 studies identified.

Table 1: Results of final search showing final search string used and number of studies identified in each database. For a more detailed final search, see Appendix 1.

FINAL SEARCH STRING USED: ("high blood pressure" OR hypertens* OR "elevated blood pressure" OR "blood pressure" OR systolic OR diastolic) AND ("probiotic supplement*" OR probiotic* OR lactobacill* OR bifidobacter* OR saccharomyces* OR enterococcus* OR streptococcus*)			
Database Searched	**Date Searched**	**Search Limiters**	**No. Results**
MEDLINE ONLY	26th July 2020	January 2014–July 2020 Plus related words Plus equivalent subjects Plus Boolean/phrase search mode	550
CINAHL complete only	26th July 2020	January 2014–July 2020 Plus related words Plus equivalent subjects Plus Boolean/phrase search mode	191
Cochrane Library Central	26th July 2020	Date January 2014–July 2020 Selected trials All years Title Abstract Keyword - with Publication Year from 2014 to 2020, with Cochrane Library publication date Between January 2014 and July 2020, in Trials (word variations have been searched)	212
TRIP database	28th July 2020	2014-2020 Only searched primary research	122
		TOTAL identified studies	1075

Databases searched

To conduct a comprehensive search, databases selected were those that focused on healthcare and scientific trials; namely CINAHL, Medline, Cochrane Library Central and TRIP.

Inclusion and exclusion criteria (IC & EC) and screening of studies

BP is often measured as a secondary outcome where participants have cardiovascular health issues such as hypercholesterolemia, so these studies were included, however those with other potential confounding conditions such as diabetes or pregnancy were excluded. Since the review is intended to inform clinical practice, strain and dosage of probiotic were criteria to be included. To minimize bias any declared conflict of interest resulted in exclusion. Identified studies were initially screened manually based on title and abstract. Duplicate studies were removed and remaining relevant full text studies were screened against pre-defined eligibility criteria (Table 2) as described below using a customized version of a Cochrane study eligibility form [29]. Unfinished/not yet published trials were excluded upon screening. The refined searches were summarised in a PRISMA flowchart [30,31] (Figure 1). Reference lists of selected studies were hand trawled to yield any further relevant studies [32].

Table 2: Inclusion and exclusion criteria applied to identified studies.

Inclusion Criteria	Exclusion Criteria
Primary data in form of RCTs on humans	Studies in children (<18years)
Studies conducted since Jan 2014	Patients had underlying health conditions such as diabetes or pregnancy
Strain and dosage of probiotic stated	Secondary literature e.g. reviews, conference proceeding, systematic reviews
Peer reviewed	Declared conflict of interest
Human participants	
English language	

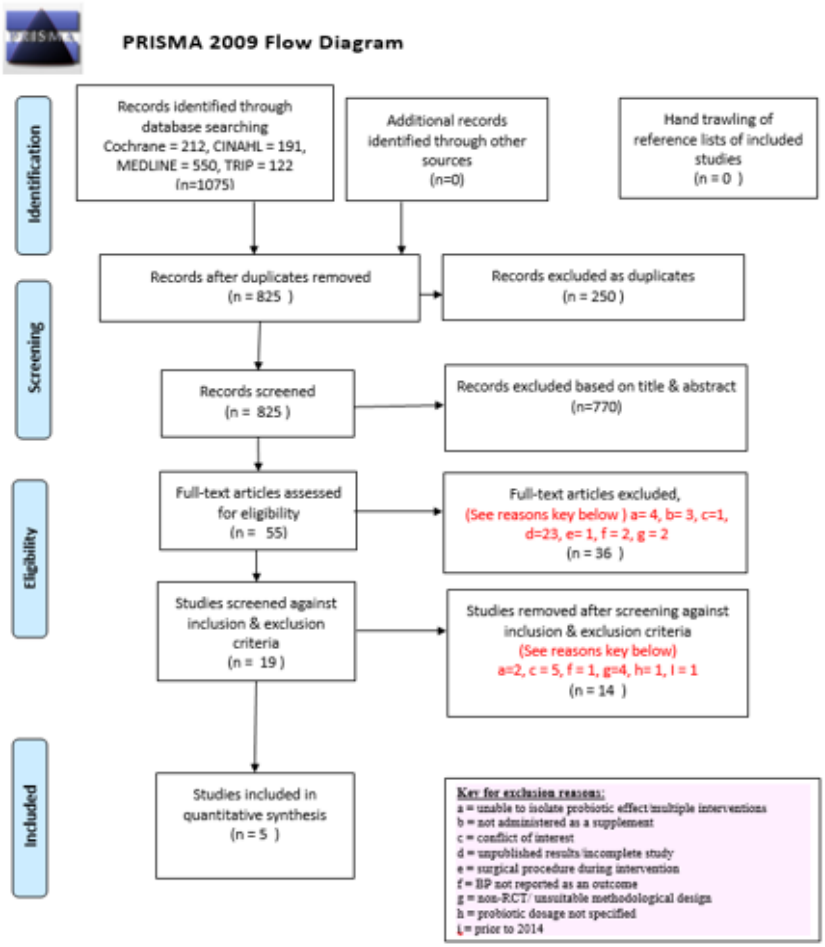


Figure 1: PRISMA flow chart depicting the stages in this systematic review with numbers of studies identified and reasons for exclusions [25].

Ethics

This study involved no direct contact with human participants, however in accordance with the University of Worcester Ethics policy, all studies included had been ethically approved and informed consent of participants was acknowledged in the study details.

Data extraction and critical appraisal of selected studies

A customised data extraction form was used based on a Cochrane tool [33,34] and data including patient demographics, sample size, probiotic strain and dosage, setting, baseline and post-intervention blood pressure were tabulated in the results section. Each publication was critically appraised using the following tools: The Cochrane Risk of Bias (RoB2) tool and Joanna Briggs Institute (JBI) Critical Appraisal tool. Once reviewed, methodological quality and risk of bias assessment were graded to produce an evidence profile (EP) displayed as a stellar chart. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [35] was used as a basis for an evidence statement.

Results

The final literature search from January 2014 to July 2020 identified 1075 studies. Following removal of duplicates and screening against eligibility criteria, five RCTs, with 453 participants in total, were included in the final analysis (Figure 1).

Study characteristics

The main characteristics of the included studies are summarised below (Table 3). For a more detailed table of key characteristics see Appendix 2. Forthwith, studies will be referenced according to their number in the table below:

Table 3: Summary of main characteristics of included studies.

Study number, Author, date Aim of study	Study design and country	Population characteristics, age (years), health status, sex Total at start of trial, Final total analysed (No. of intervention participants/No. of control participants)	Blood pressure level for inclusion in trial (mmHg)	Pre-specified sample size statistically calculated	Method of randomisation for allocation to treatment	Duration of follow-up (weeks)	Probiotic intervention	Placebo similar to intervention
1. Ivey et al., 2014 **Effect of yoghurt and probiotics on blood pressure and serum lipid profile**	Double blind, parallel, factorial RCT Australia	Over 55yrs, overweight, males and females **Total at start 156** (79 intervention/ 77 control) **Total in final analysis 156** (79 intervention/ 77 control)	≥120/80mmHg	yes	Random number generation	6	Dual species	Contents not specified. Identical appearance.
2. Rerksuppaphol and Rerksuppaphol, 2015 **Efficacy of two probiotics on reduction of serum cholesterol in hypercholesterolaemics**	Double blind, placebo controlled RCT Thailand	40-60yrs, hypercholesterolaemic, both sexes, **Total at start 66** (33 intervention /33 control) **Total in final analysis 64** (31 intervention/33 control)	Not specified	yes	Computer generated	6	Dual species	Contents not specified. Identical appearance.
3. Ibrahim et a.l, 2017 **Effect of combined probiotics and circuit training on muscular strength, power and cytokine responses in young males**	Randomised, parallel, placebo controlled trial Malaysia	19-26 years, healthy, sedentary males **Total at start 48** (24 intervention/24 control) **Total in final analysis 41** (19 intervention /22 control)	Not specified	Not specified	Not specified	12	Multispecies and multistrain	Identical apart from no bacteria.
4. Möller et al., 2017 **Influence of acute multispecies and multi-strain probiotic supplementation on cardiovascular function and reactivity to psychological stress in young adults**	Parallel groups, Double blind RCT USA	18 -23yrs healthy student volunteers, 89% white, 69% female **Total at start 123** (67 intervention/56 control) **Total in final analysis 105** (57 intervention/48 control)	Not specified	Not specified	Random number generator	2	Multispecies and multistrain	Corn-starch capsule of similar appearance

5. Lee et al., 2017 **No additional cholesterol lowering effect observed in the combined treatment of red yeast rice and Lactobacillus casei in hyperlipidaemic patients: a double-blind randomised controlled clinical trial**	Double blind randomised controlled trial China	40-60 hyperlipidaemic patients, 76% male **Total at start 60** (30 intervention/30 control) **Total in final analysis 55** (27 intervention/28 control)	Not specified	Yes	Computer generated random number	12	Single species	Starch capsule

Overview of included studies

Included studies were RCTs with four (1, 2, 4 & 5) reporting a double-blind design, with detailing in studies 2, 4 and 5. Two studies (2 & 4) measured the effect of the probiotic supplement (intervention) upon a number of outcomes including BP. The other three (1, 3 & 5) had a factorial design investigating other interventions alongside probiotic supplementation, but required data was extracted without contamination from the total data. Study 5 did not report final BP measurements but did include change in BP (Table 4). Sample size ranged from 48 (study 3) to 156 (study 1) with studies 3 and 4 experiencing greatest loss to follow up. Trial duration ranged from two to 12 weeks. Two studies (3 & 4) recruited young (18-26 years) volunteers, whilst the remaining studies (1, 2 & 5) used participants aged over 40 years. Studies 2 and 5 recruited hypercholesterolemia/hyperlipidemic participants from hospital clinic settings respectively, whereas two other studies (3 & 4) recruited from a university setting. Study 1 recruited randomly from the electoral roll. Baseline characteristics were well matched for each cohort in each study. All studies reported use of a placebo identical in appearance to the probiotic.

Table 4: Details of intervention and placebo, BP measurements pre- and post-intervention with findings.

Study number and title	Probiotic Contents (CFU)/day	Placebo contents	Intervention baseline mean BP measurements mmHg ± SD Post intervention baseline measurements shown in red Change in BP shown in green	Control baseline mean BP measurements mmHg ± SD Post intervention baseline measurements shown in red	Findings
1. Ivey et al., 2014	L. acidophilus La5 B. animalis subsp. Lactis Bb12 (3.0×10^9 CFU)	Not specified	Probiotic (plus yoghurt) SBP 131 ± 13 SBP 131 ± 14 DBP 74 ± 11 DBP 74 ± 10 Probiotic (plus milk) SBP 132 ± 12 SBP 130 ± 12 DBP 76 ± 10 DBP 75 ± 9	Placebo (plus yoghurt) SBP 130 ± 12 SBP 129 ± 11 DBP 74 ± 7 DBP 75 ± 7 Placebo (plus milk) SBP 130 ± 12 SBP 129 ± 13 DBP 74 ± 7 DBP 73 ± 8	No evidence to support probiotic supplements exhibiting anti-HT effect when compared to control milk or placebo capsules (p>0.05)
2. Rerksuppaphol and Rerksuppaphol, 2015	L. acidophilus (minimum 10^9 CFU) B. bifidum (10^9 CFU)	Not specified	SBP 139.5 ± 24.4 SBP 131.6 ± 20.4 DBP 87.7 ± 16.5 DBP 84.0 ± 14.9	SBP 130.8 ± 0.07 No sig difference DBP 82.7 ± 8.8 No sig difference	Significant decrease in SBP in probiotic group (p= 0.01) No significant change in DBP in probiotic group

3. Ibrahim et al., 2017	L. acidophilus L. casei L. lactis B. bifidum B. infantis B. longum Total 6 x 10^{10} CFU (2 sachets) Plus other nutrients (carbohydrate, lactose, sugar, protein, fat and fibre).	No bacteria. Nutrient content as in probiotic.	Probiotic (+ sedentary) SBP 120.7 ± 3.4 SBP 121.4 ± 3.0 DBP 68.6 ± 2.4 DBP 71.0 ± 2.2 Probiotic (+ circuit training) SBP 121.0 ± 3.8 SBP 121.8 ± 3.3 DBP 71.4 ± 2.4 DBP 71.1 ± 3.5	Placebo (+ sedentary) SBP 117.6 ± 3.7 SBP 120.0 ± 2.7 DBP 70.4 ± 1.1 DBP 71.8 ± 1.5 Placebo (+ circuit training) SBP 118.0 ± 3.2 SBP 120.0 ± 2.4 DBP 70.7 ± 1.5 DBP 69.1 ± 3.1	BP not specifically discussed, however recorded other parameters (including SBP and DBP) were not significantly affected and tabulated results show no effect of probiotic supplementation on BP in either intervention groups
4. Möller et al., 2017	B. breve B. longum B.infantis L. acidophilus L. plantarum L. paracasei L. bulgaricus Streptococcus thermophilus 112.5 x 10^{9} CFU	Cornstarch	SBP 115.08 ± 13.71 SBP 115.25 ± 13.85 DBP 68.44 ± 6.61 DBP 68.16 ± 7.40	SBP 115.83 ± 13.12 SBP 115.20 ± 13.43 DBP 69.22 ± 5.64 DBP 68.35 ± 6.12	No significant effect from probiotic supplementation on SDP or DBP (p>0.05)
5. Lee et al., 2017	Lactobacillus casei 1x10^{8} CFU twice daily Plus Lovastatin 5.7mg, GABA 6.8mg (metabolite from red yeast rice), Citrinin <1.0 µg/ml	Starch Plus Lovastatin 5.7mg, GABA 6.8mg (metabolite from red yeast rice), Citrinin <1.0 µg/ml	SBP 141.50 ± 24.52 Change in SBP Week 4 -1.96 ± 17.68 Week 8-5.70 ± 19.51 Week 12-5.04 ± 15.82 DBP 85.00 ± 15.48 Change in DBP (at week 12) Decrease of 2.67	SBP 134.20 ± 18.61 Change in SBP Week 4 1.86 ± 22.39 Week 8-0.68 ± 18.32 Week 12-1.79 ± 14.17 DBP 79.31 ± 12.53 Change in DBP (at week 12) Increase of 4.43	Reduction in SBP, but not statistically significant. Statistically significant reduction (p<0.05) in DBP seen in probiotic group.

Key findings

The table above (Table 4) presents details of intervention, placebo and key findings of each included study.

Studies 2 and 5 report a clinically significant decrease in either SBP (study 2) or DBP (study 5) in the probiotic cohort. It is important to note that the intervention cohort in both of these studies (2 & 5) had elevated baseline BP (study 2: SBP 139.5 ± 24.4 mmHg, DBP 87.7 ± 16.5 mmHg; study 5: SBP 141.50 ± 24.52 mmHg, DBP 85.00 ± 15.48 mmHg) compared to the placebo group (study 2: SBP 130.8 ± 0.07 mmHg, DBP 82.7 ± 8.8 mmHg; study 5: SBP 134.20 ± 18.61 mmHg, DBP 79.31 ± 12.53 mmHg) placing the intervention cohorts in the high pre-HT range [36] and, interestingly, only the probiotic groups in these studies (2 & 5) reported a significant decrease in BP. Contrastingly three studies (1,3 & 4) reported no significant effect upon BP following probiotic supplementation. Study 1 found no effect of the probiotic upon BP and reported mean baseline SBP as 131 (±12) mmHg placing it in the mid pre-HT range, however mean baseline DBP at 74 (±9) mmHg was normotensive. Studies 3 & 4 both had normotensive cohorts at baseline. The possible implication of this is baseline BP may be an important consideration. Findings are discussed as a critical analysis of the studies and the weighting given to their evidence.

Methodological quality and risk of bias assessment

Results of CA and RoB assessment are summarised below (Tables 5 & 6).

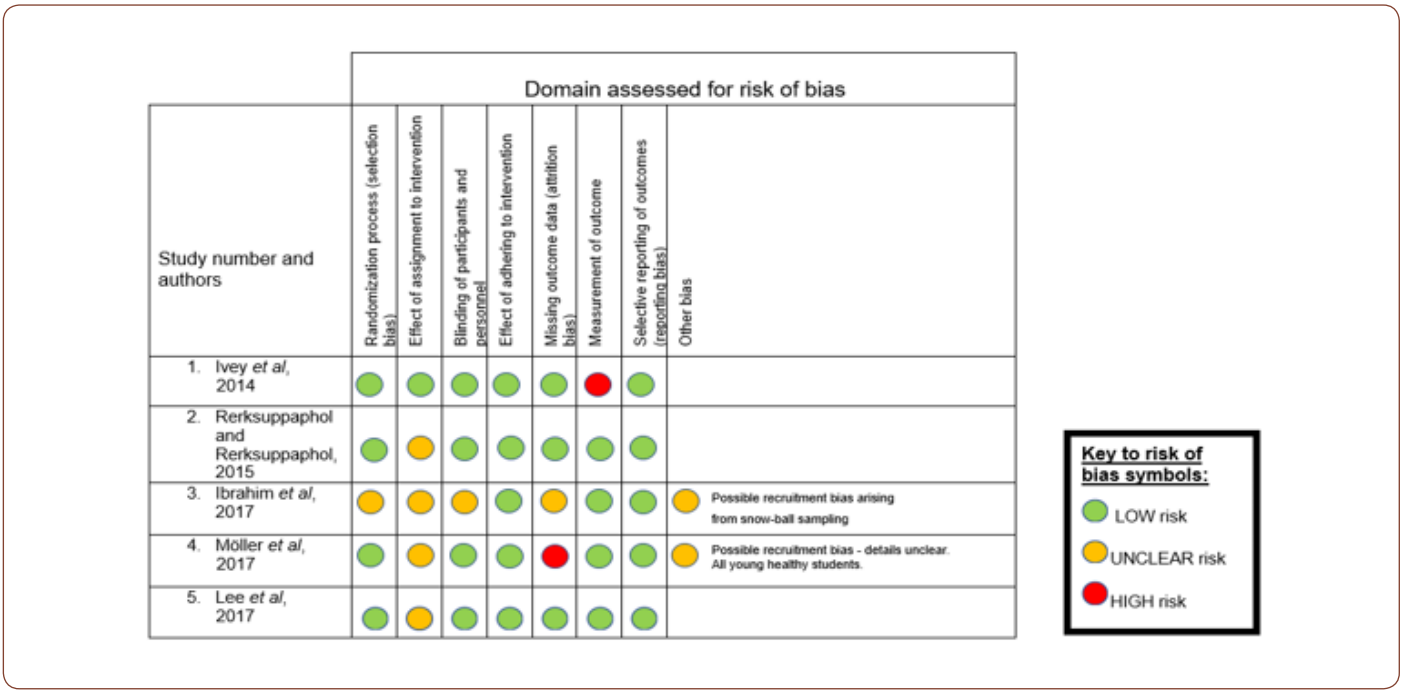
Table 5: Critical appraisal of included studies.

Study number and citation	Strengths	Limitations
1 Ivey et al., 2014	• Clear and justified research value • Eligibility criteria described • Large sample size (n=156) • Reported effect of probiotic supplementation on BP and p-value reported • Consumption of probiotic supplement standardised (30 minutes prior to first meal of the day) in all participants • Placebo and probiotic identical in appearance • 3 week wash out period prior to intervention and refrained from consuming probiotic foods before and during trial • Detailed description of BP measurement, taken bi-daily and standardised. Cross referencing of BP records between machine and self-recordings. • Random recruitment from electoral roll • BP ≥120/80mmHg as inclusion criteria so participants have elevated BP • Sample size calculated for effect size and power (80%) • Possibility of interactions of interventions was evaluated to minimise confounding • Home monitored BP – more realistic setting for participants • Baseline cohort characteristics well matched • BP measured at similar times of day to standardise	• Limited details of randomization procedure • Slightly more males than females in groups and all participants overweight limiting generalizability • Older age group (>55yrs) • Short trial period (6wks) • BP measured and self-reported at home not by health professional so potential confounding • Factorial study so milk/yoghurt consumption may confound • Possible attrition bias as no impact analyses of those lost to follow up and no reasons given. • Compliance not recorded • No confidence intervals • No mention of calibration of BP machines • No details of blinding procedure • Highly strain-specific probiotics used
2 Rerksuppaphol and Rerksuppaphol, 2015	• Clear and justified research objective • Eligibility criteria described • Compliance monitored and was high level especially in probiotic group (>94%) and comparable between groups • Sample size calculated by statistical analysis (80% power) • BP recorded by health professional (nurse) • Avoided probiotic foods during trial excepting intervention and 12 hour overnight fast before trial • Blinding procedure discussed • Blinding complete until after study • Randomisation sequence revealed after completion of study • Low drop out	• No absolute BP values in placebo group only reported as "no significant changes" on SBP or BBP • Higher BP in probiotic group at baseline though not significantly so • BP was secondary outcome – less emphasis potentially upon measurement of outcome • No confidence intervals • Participants recruited from hospital clinic so may not be generalisable as already undergoing treatment/ other health issues • Per-protocol analysis rather than ITT so possible risk of bias as some participants missing from final analysis • Participants mainly female limiting external validity • Some side effects (mainly in probiotic group) • Short duration of trial (6 wks) • Diet not controlled or monitored with respect to probiotic foods throughout trial • Small sample size (n=66) • No impact analysis of loss to follow up

3 Ibrahim et al., 2017	• Clear and justified research objective • Eligibility criteria described • High compliance and adherence (> 95%) • Identical placebo • Long duration of trial (12 weeks)	• Recruitment by snowball sampling – difficult to determine sampling error. • No details on allocation concealment. • No statistics conducted on inter-group baseline characteristics to ascertain any inter-group variation • No details regarding integrity of delivery/blinding process • No details regarding measurement of outcome • No power or effect sizes calculated. • Small sample size (n=48) • Young healthy males so not generalizable • Unclear on allocation – possible bias effect of assignment to intervention. • High loss to follow up (14.5%) • Possible attrition bias as ITT analysis not carried out • Evidence of per-protocol analysis • No confidence intervals • BP was secondary outcome so very limited discussion of it • Other nutrients in capsules may present potential confounding
4 Möller et al., 2017	• Food frequency survey used to assess consumption of probiotic foods. • Probiotics & placebo refrigerated to preserve viability • High integrity of delivery – double blinding. • Group allocation revealed after conclusion of study • 3 BP readings taken and averaged. • Random assignment method is transparent • Details of blinding procedure given • Compliance recorded and equivalent in both groups • Blinding broken after completion of data collection • Antibiotic use was an exclusion criterion	• No details of inclusion criteria • Recruitment method may introduce selection bias as student volunteers • Very short trial period (2 weeks) – limited treatment period • Some side effects – stomach ache & bloating (intervention group), headache and rash in placebo group • Young, predominantly white female participants – lacks external validity • Possible attrition bias due to high loss to follow up and failure to use ITT analysis. • Larger final analysis sample in probiotic group (n=57) versus placebo group (n=48) • Some missing outcome data missing due to side effects in participants and equipment malfunction • Participants were not asked to avoid potentially probiotic foods e.g. yoghurt. No attempt to control other sources of probiotic in diet so may have introduced confounding. • High participant loss to follow up (15%) especially in probiotic group • Participants generally healthy and NT at outset • No confidence intervals stated

5. Lee et al., 2017	• Clear and justified research objective • Eligibility criteria described • Identical placebo • Long duration of trial (12 weeks) • Effect size calculated (>95% power) • Double blinding and randomisation described in detail	• Factorial design as also gave red yeast rice, but able to isolate effects of probiotic from data • Participants recruited from hospital clinic so may not be generalisable as already undergoing treatment • Per-protocol analysis rather than ITT so possible risk of bias as some participants missing from final analysis • No dietary details • Patients 40-60 years so may not be generalisable to other age groups • Absolute BP outcomes not reported (however change from baseline is) • No confidence intervals

Table 6: Summary of RoB assessment of selected studies as assessed using RoB2 tool [78].



Critical analysis of included studies: Following CA and RoB assessment, it was evident that methodological quality varied between the included studies and this is detailed below.

Stronger methodological design: Three studies (1, 2 & 5) emerged as being stronger in methodological design with lower risk of bias. These were the only studies that included either pre-HT or HT participants at baseline and two of these studies (2 & 5) reported reduced BP following probiotic intervention, whilst study 1 reported no effect of the probiotic upon BP. Studies (2 & 5) supporting the intervention will be discussed first.

Study 2: Study 2 was appraised overall as high quality with low RoB, but some weaknesses were identified. Firstly, the relatively short intervention period of six weeks was regarded as a potential limitation since more effective retention of bacterial colonies have been observed with longer intervention periods [37]. Secondly there was some lack of clarity regarding assignment of intervention as some participants withdrew so it is difficult to ascertain if bias was introduced. Thirdly generalizability may be restricted as recruitment was from a clinic setting and participants had other health issues (hypercholesterolemia) [38].

Notwithstanding these potential limitations, this study was judged to be of high methodological quality for the following reasons. The study was sufficiently powered (80%) with pre-calculated sample size beforehand to ensure a high chance of detecting a statistically significant effect and avoiding a possible type 2 error [38]. There was high adherence to the intervention (>90% in both groups) and control of potential confounders by avoidance of probiotic food sources throughout the trial. Furthermore, measurement of outcome by a health professional was judged to possess high integrity. In summary, the overarching

strengths of this study, namely high integrity and detailing in its methods, sufficiently powered calculation of effect size and minimization of confounders identified this as a robust study, which was consequently weighted highly, and would be further improved if conducted for a longer duration on a larger sample size.

Study 5: Some design shortcomings were identified, one being using Last Observation Carried Forward (LOCF) approach in final data analysis, which can introduce bias and distort findings [39]. Additionally, recruitment from a hospital clinic can potentially limit external validity [38]. However, despite these drawbacks, this study exhibited thorough pre-planning and transparency throughout; pre-specified highly powered sample size was calculated in advance, randomisation, allocation to intervention and probiotic therapy administration were detailed and explicit. Hence, this study was judged to provide good quality evidence and awarded higher weighting.

Study 1: Although considered overall to be a strong study, lack of clarity in the description of the methods of allocation to intervention and blinding deemed it impossible to judge whether there was an element of selection bias. Furthermore, it could be argued that in a home setting a high risk of bias may have been introduced in the measurement [40] owing to confounding by other factors in the home, for example alcohol consumption [41]. Notwithstanding these potential shortcomings, study 1 benefits from random recruitment from the electoral roll increasing external validity and minimizing recruitment bias [38]. Its methods were detailed and transparent with a pre-specified large (n=156) sample size to ensure sufficient power. Additionally, a three-week pre-intervention washout period and avoidance of probiotic foods throughout the trial sought to minimize confounding. Finally, this was the only study to study BP as a primary outcome so was highly relevant to the research aim. Overall, it was well conducted and consequently, weighted highly as evidence.

Weaker methodological design: The remaining included studies (3 & 4) were judged to be of lower quality evidence for reasons discussed below and, hence, awarded less weighting.

Study 3: A main limitation of study 3 was an absence of statistical analysis such as calculation of effect size and sample size was small (n=48) with a high loss to follow-up (>14%). Taken together it was impossible to know if this study was sufficiently powered [38]. Recruitment bias was also a potential concern as participants were recruited from a university setting by snowball sampling [38] making it difficult to determine the presence of sampling error or make inferences about populations. Furthermore, the study comprised of healthy young males (100%), restricting generalizability. Assessment of bias was hindered by a general lack of transparency in allocation to treatment and blinding procedure [38]. Despite the aforementioned limitations, study 3 does possess some merits namely a long trial period (12 weeks) allowing time for bacterial colonization to establish [42] and high adherence to the intervention (>95%). Overall, these weaknesses in design suggest that the findings should be interpreted with caution, hence this study was given less weighting.

Study 4: Many procedures in this study such as randomisation, blinding and administration of intervention exhibited high integrity and statistical analysis was conducted prior to the intervention. However, the recruitment setting diminished the external validity of results [38]. Furthermore, success of colonization and retention of the probiotic is questionable owing to the short timescale of two weeks [38,43]. Despite a large sample size (n=123), effect size was not pre-calculated and large loss to follow-up (15%) was reported, especially in the intervention group, which may skew the results [38,44,45]. Finally, this was the only study not to avoid extraneous probiotic foods during the trial potentially introducing confounders. In view of these limitations, this study was considered to provide low evidential value and less weighting was given to it.

A criticism of all the studies lies in the final analysis of results. The Consolidated Standards of Reporting Trials (CONSORT) [46] statement relating to RCTs recommends results are analysed based upon Intention to Treat (ITT) strategy meaning when conducting a comparison trial (probiotic vs placebo), participants who withdraw during the trial should be included in the final analysis [47] to reduce bias, which is often in favor of the intervention, especially when sample size is small [48]. Studies 1, 3, 4 and 5 carried out a per-protocol analysis, which omitted results from those lost to follow up in the final analysis, whilst study 2 did not report the analysis method. Disregarding "non- adhering" participants in a RCT undermines the principle of randomisation and makes it hard to draw valid comparisons between trial arms [49]. ITT analysis in RCTs is, therefore, regarded as an indicator of good practice [50]. Furthermore, lack of statistical analysis of results was evident in all five studies compromising methodological quality and potentially diminishing the statistical power of the results. Nevertheless, these studies did fulfil the stringent screening and selection process of this LR and the quality of their evidence will be discussed in the next section.

Overall quality of evidence assessment

Following CA, a number of criteria that determine methodological quality and risk of bias have been graded from very low to high (grades 1-4) across the studies (see Appendix 3), to generate an evidence profile (EP). RCT study designs are regarded as high-quality evidence [44,45] so were graded 4 for study design. Gradings were converted to a graphical representation (stellar chart) of the EP where the increasing length of each "spoke" of the "star" corresponds to increasing quality of evidence as below (Figure 2).

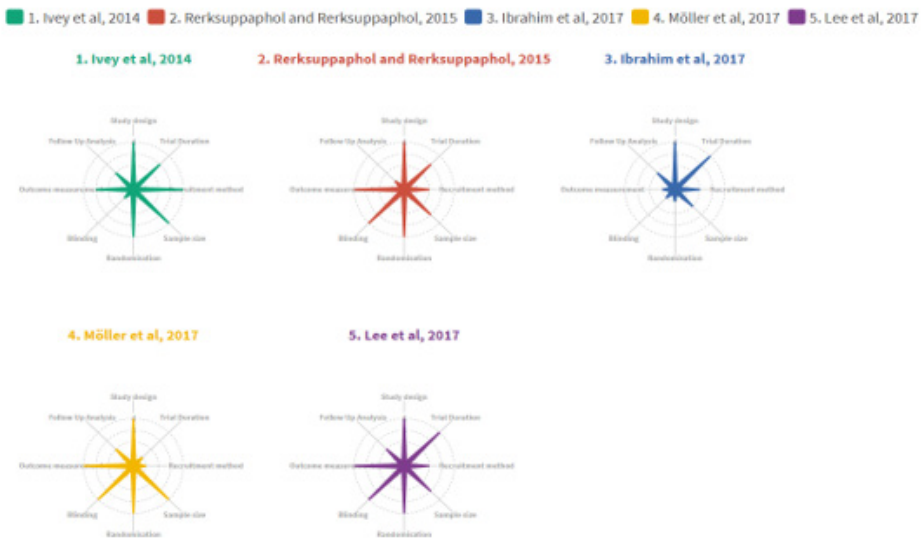


Figure 2: Quality of evidence profiles of included studies visualised as stellar/radial bar charts. (Image created using Flourish visualisation software).

The stellar charts clearly show studies 1, 2 and 5 as high quality in most of the domains assessed, thereby increasing confidence in recommendations based on their findings. Contrastingly studies 3 and 4 displayed shortcomings in at least three domains so their findings were given less weighting.

Evidence statement

This research study presents moderate evidence based upon National Institute for Health and Care Excellence (NICE) guidelines [51] (see Appendix 4), from two robust studies (2 & 5) suggesting a net benefit of probiotic supplements in reducing BP. If the methodologically weaker studies (3 & 4) are excluded, the balance of evidence strengthens further towards probiotic supplementation being beneficial for HTN reduction. However, further research with larger scale trials using target groups such as pre-HTs/HTs for longer duration is recommended.

Discussion

Statement of findings

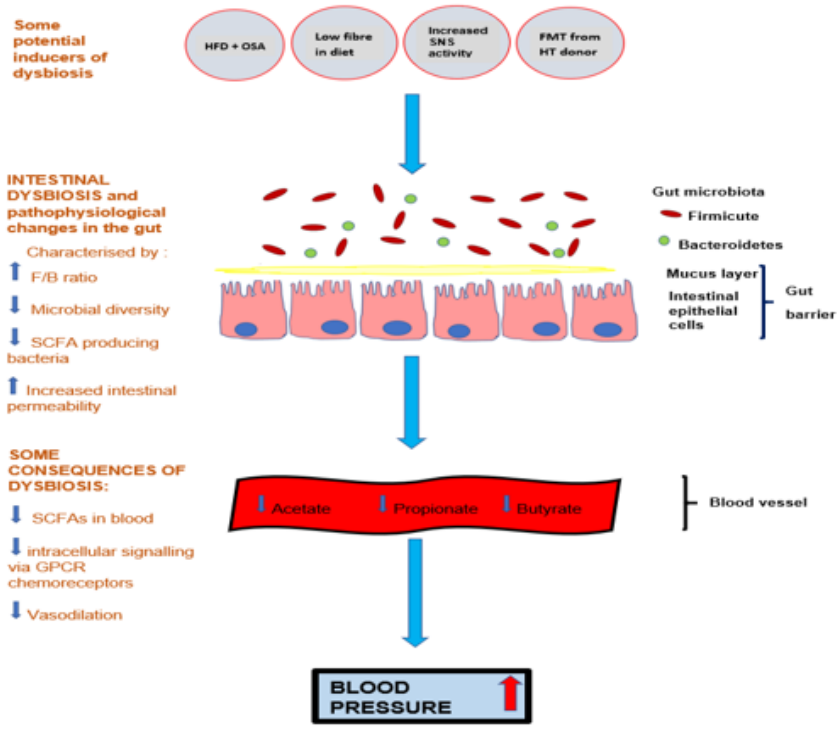
Two of the studies (2 & 5) observed a significant decrease in BP in the probiotic groups. Importantly, the probiotic cohorts of these studies had a higher mean baseline BP compared to the control group and classified as pre-HT and HT respectively [52]. The third study (1) composed of participants with mid pre-HT SBP and normotensive DBP at baseline and reported no effect of probiotic supplements on BP. This systematic literature review, therefore, adds to the growing body of research [22,53,42,54] indicating that baseline BP status prior to intervention may be influential upon the efficacy of the probiotic supplement.

Although included studies of this LR did not conduct GM analysis, and so it is impossible to determine whether dysbiosis was an underlying condition, wider research suggests its role in pathogenesis and maintenance of HTN [19,20,55-57].

Dysbiosis association with HTN

Existing evidence appears to support an association between gut dysbiosis and elevated blood pressure. The precise aetiology of HTN remains elusive and risk factors are multifaceted [58], however, as aforementioned, a disrupted gut microbial profile has been identified as a possible driver [20,25,56,59]. Whilst individual GM are dynamic and variable, HTs have been shown to exhibit an inverse relationship between microbial diversity and HTN [19]. A seminal study by Durgan DJ, et al. [60], in animal models demonstrated that dysbiosis causes HTN. A causal link between the GM and HTN is further supported by faecal microbiota transplantation (FMT) studies in animal and human models. Microbiota from HT donor rats was able to induce HTN in NT recipients [55,60,62]. Transferability of HBP through FMT from HT humans' microbiota to germ free (GF) mice has also been demonstrated [59]. Taken together these results suggest the GM is susceptible to manipulation and may offer a potential therapeutic focus for HBP management. A further important finding is that dysbiosis appears to precede the development of HTN. Prehypertension (pre-HTN) is defined as a BP of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg [61]. GM analysis shows minimal variation between pre-HT and HT microbial profiles in both animal and human models, but were distinctly altered from a NT GM [56,59] (suggesting that in pre-HTN dysbiosis has already occurred. Collectively, these findings suggest that ideally interventions to restore GM balance should commence at an early stage to prevent HTN. Although further research is required to clarify mechanisms through which the GM influences BP, the following section outlines hypotheses.

How dysbiosis may induce HTN: Bacterial metabolic by-products may be important signalling molecules for BP. Short chain fatty acids (SCFAs), predominantly acetate, propionate and butyrate are produced during bacterial fermentation of dietary fibre in the colon [62,65] mainly by Firmicutes and Bacteroidetes phyla [66]. Whilst functional pathways are yet to be elucidated and specific bacterial genera of bacteria are not yet confirmed, SCFAs are thought to act as important signalling metabolites between the GM and BP [65-68]. Murine studies suggest SCFAs may signal via specialized chemoreceptors found in locations associated with BP regulation, including the walls of blood vessels and kidney tissue [65] known as G protein-coupled receptors (GPCRs) [65,67]. Moreover, depletion of some SCFA-producing bacteria, as observed in dysbiosis, are associated with development of HTN [67,69-72]. Induction of HTN in rat models correlated with reduced butyrate-producing bacteria and downregulation of butyrate metabolisms [60], whilst acetate supplementation correlated with a reduction in dysbiosis, observed as a reduced F/B ratio and reduced BP in HT animals [69,71]. Notwithstanding the limited human research, from these findings it could be hypothesized that a gut microbial shift may alter metabolite production, such as SCFAs, which may impact BP regulation as summarised in Figure 3.



Abbreviations HFD: High fat diet; OSA: Obstructive sleep apnoea; SNS: sympathetic Nervous System; HT: Hypertensive; FMT: Faecal Microbiota Transplantation; GPCR: G protein-coupled receptors; F/B ratio: Firmicutes/Bacteroidetes ratio; SCFA: Short chain fatty acids
Figure 3: Summary diagram of possible inducers of dysbiosis, their effect upon gut microbiota, consequential SCFA production and signalling culminating in elevated BP.

Dysbiosis facilitates inflammation: Other studies suggest the presence of gut microbiota appears necessary for HTN to develop possibly by facilitating inflammation [73], which underlies HTN [56,57,69]. HT human participants in a small Brazilian study were found to have dysbiosis and an inflamed immune profile compared to their NT counterparts [58]. Additionally, several SCFA (mainly butyrate) producers were diminished in the HTs [57]. Juanola O, et al. [72], also report diminished levels of SCFAs associated with an inflammatory profile and HTN. Although based on relatively limited samples, these findings suggest interplay between the GM, HTN and the immune system. Consequently, interventions targeting the GM, such as probiotics, may offer anti-HT potential. A number of physiological mechanisms by which probiotics may influence blood pressure are explored below.

Modulation of dysbiosis: A causal link has been demonstrated between dysbiosis and HTN [60]. Probiotics in HT rat models have been seen to ameliorate dysbiosis by reducing an elevated F/B ratio and increasing SCFA producers along with an accompanying decrease in BP [75], however they appeared ineffective on NT animals [71,75], which may imply an absence of dysbiosis. Although not human studies, these results appear to support the findings of this LR, which suggests that probiotic supplements are only effective when BP is elevated. A possible reason for this is that the HBP was driven by dysbiosis so that restoration of microbial balance by the

probiotics ameliorated the HTN. Interestingly, study 1 appeared unresponsive to probiotics, which could be related to baseline BP status. This study (1) cohort was marginally pre-HT for SBP, but NT for DBP from which it could be inferred that dysbiosis was either absent or not sufficiently advanced to cause HTN. Further studies utilizing GM analysis would be useful to establish whether HTs have dysbiosis prior to probiotic intervention and the impact on the GM and BP post-intervention.

Anti-inflammatory effect and upregulation of NO improve Endothelial Function: Probiotics may reduce pro-inflammatory status and related endothelial dysfunction. Inflammation has been shown to be strongly associated with HT [57] and associated impairment of endothelial function possibly by reduction of Nitric Oxide (NO), a vasodilator [76]. Lactobacillus strains administered to SHR appear to reduce inflammatory status and upregulate bioavailability of NO, thereby improving endothelial function [76]. It is of interest that the studies used in this LR all included lactobacillus strains, but not all reduced BP suggesting other conditions may need to be present, such as dysbiosis. In conclusion, this LR provides moderate evidence for efficacy of probiotic supplements in reducing HTN. In arriving at this judgement, the presence of elevated BP at baseline is an important factor along with the relative quality of evidence from five included studies.

Evaluation of included studies

This literature review found moderate evidence for the efficacy of probiotic supplements in reducing HTN. In arriving at this judgement, the presence of elevated BP at baseline is an important factor along with the relative quality of evidence from the five included studies. Only three studies (1, 2 & 5) of the five included participants with either HTN or pre HTN prior to intervention. Two of the studies (2 & 5) are particularly relevant to the research aim as their participants had baseline BP ≥130/85mmHg, which has been found to produce a more significant reduction with probiotics than baseline BP below these values [22] and are more generalisable to clients likely to be encountered in a clinic setting. Study 2 on pre-HT participants (mean baseline BP 139.5/87.7mmHg) demonstrated improved SBP following probiotic supplementation. Despite some limitations following CA, as discussed previously, this study was considered to be of particular value to the research as it used participants with elevated BP at the outset. Study 5 also reported a significant reduction in DBP in the HT cohort (mean baseline BP was 141/85mmHg). Notwithstanding the limitations discussed previously, this highly powered study was of good methodological quality, so its findings are highly weighted. If, as research suggests, dysbiosis is causal in HTN [19,57,60], then one possible explanation for the findings in studies 2 and 5 may be that participants had imbalanced gut microbiota, which was restored by administration of the probiotic and so reduced the BP, however without GM analysis, this remains hypothetical. Contrastingly, Study 1 reported opposing findings as despite the participants having only elevated SBP (131± 13mmHg), probiotics did not lower BP. Although critically appraised to be a high-quality study, there are a number of factors that may account for non-effect of the probiotic. Firstly, other literature has suggested consumption of probiotics may have a greater effect when baseline BP is borderline HT [22,42,54] with Khalesi S, et al. [23], noting a significant reduction if BP ≥ 130/85mmHg. As the SBP in study 1 was only marginally raised, the effect of the probiotic, if any, may have been insignificant. A second important factor to consider is that strain specificity of probiotics may affect efficacy. Study 1 used a two-strain preparation containing Lactobacillus acidophilus La5 and Bifidobacterium animalis subsp. lactis Bb12, which have been reported as less effective in other trials [76]. Furthermore, anti-HT effect appears more significant when daily dose is >5 x109 CFU/day with an intervention period ≥8 weeks [42]. Study 1 used 3 x109 CFU/day for 6 weeks. Collectively these factors could mean both strains, dosage and duration were sub-optimal in study 1 to see any effect of the probiotic. Thirdly the participants in study 1 were overweight so it is possible that this was a factor in their elevated SBP rather than dysbiosis in which case probiotic consumption may have had little benefit. Several issues, therefore, emerge from study 1 that remain unclear. Without GM analysis, it is impossible to ascertain whether dysbiosis was present. Furthermore, as the DBP was not elevated and SBP was marginally pre-HT, if present, dysbiosis may not have been sufficiently advanced to have yet impacted upon BP, hence the failure to observe a response to the probiotic. Therefore, on the strength of the most robust evidence of studies 1, 2 and 5, probiotic supplements do appear to reduce BP with the caveat that the participants are HT at baseline. The other two included studies (3 & 4) were judged to be of lower quality and, importantly, were conducted upon normotensives. When these weaker studies are disregarded, the findings of this LR lend further support for the use of probiotic supplements to reduce BP in HTs. However, they indicate a need for further research using longer duration studies on HTs with specific strains of probiotics administered in capsule form. A minimum dosage of 5x109 CFU/day would be recommended. GM analysis at baseline and post-intervention would also be advantageous to establish whether dysbiosis is initially present and, if so, the effects of the probiotic upon the GM. Other SRs are consistent with the findings of this LR; [54], examined probiotic supplementation and found a short-term reduction in HBP. Whilst a large number (n=23) of RCT studies were included, methodological quality was variable, however an advantage was that nine studies were in HTs and, in seven of those, no HTN medication was being taken so the effects of the probiotic could be examined in isolation. Chi C, et al. [53], reported a significant reduction in SBP and DBP in HT human participants, particularly if Diabetes mellitus (DM) was present, although the anti-HT effect appeared age specific (≤ 60 years). Collectively these studies corroborate the findings from this literature review that probiotics can be of benefit in reduction of HTN and suggest further study focus should be upon dosage and strains in larger scale, longer duration trials on HT humans. The findings of LR are significant as,

although modest BP reductions were observed in this study and the wider literature, it is suggested that even a 3.3/1.4mmHg reduction may reduce risk of a serious cardiovascular event by 22% [78].

Recommendations as to the use of probiotic supplements as an intervention when supporting HT clients in a Nutritional Therapy setting

The findings of this research study suggest probiotic supplements may be a beneficial intervention for pre-HT/HT clients, particularly where dysbiosis may be suspected to be present. The following factors should be considered when recommending probiotic supplements.

Strain specificity: A lack of human trials made it impossible to definitively determine efficacy of specific strains, however Lactobacillus sp. is present in both effective studies (2 & 5), which is consistent with the wider literature [42]. A number of studies suggest multi-strain probiotics have shown effectiveness [23,53]. The recommendation, therefore, would be a multi-strain preparation including Lactobacillus species.

Dosage and duration: Study 5 suggests dosage is effective at >2 x 108 CFU/day. Other studies suggest greater benefit may be found with a larger dosage [23,42,79]. However, there is disparity in the wider literature and clients would need to be made aware of potential side effects such as bloating or abdominal cramps. Although studies 2 and 5 reported an anti-HT effect after 6 and 8 weeks respectively, a duration of at least 8 weeks is recommended in the wider literature [42].

Age: Age of client is also a consideration as this research study reported beneficial results in 40–60-year-olds, however limited benefit was observed in over 60-year-olds [53], but no adverse effects were reported either. Further research would be required to determine efficacy in different age strata.

Administration: Both studies (2 & 5) administered the probiotic in capsule form, which is in line with recommendations in other studies [42]. Although study 5 administered the supplement post-prandially morning and evening, due to the small numbers of studies it was not possible to establish the best time to take a supplement and these may vary depending upon manufacturer's guidelines.

Recommendations

In summary, it is recommended that a multi-strain probiotic including Lactobacillus species is taken for a minimum of eight weeks administered as per the manufacturer's instructions. A minimal dosage of 5 x 109 CFU/day in capsule form appears to be of most benefit in HTs below 60 years.

Overview of Study Limitations

Although the empirical studies selected for this research were all RCTs, regarded as high-quality evidence when evaluating the efficacy of an intervention, the stringent eligibility criteria applied may have excluded some studies with HT participants. Excluding studies with medical co-morbidities such as T2DM was deemed necessary to prevent confounding from other health conditions and medications. However, this reduced the scope for inclusion of studies where participants were pre-HT/HT at baseline. Furthermore, none of the studies analysed GM composition so it was not possible to know if HT participants were dysbiotic at baseline and whether any reduction in BP was due to the probiotic effect on the GM. As probiotics are a growing area of research, in retrospect, searching grey literature, such as unpublished clinical trials, may have been useful to ensure that the most recent evidence was appraised [80].

Conclusion

This study found moderate evidence that probiotic supplements can reduce HTN where baseline BP is borderline HT and supports the growing body of evidence suggesting a potential role for probiotics in reduction of HTN. The research indicates dysbiosis in the GM can be a causal factor in HTN. Probiotics may restore GM balance and increase metabolites involved in BP modulation to reduce HTN. The findings of this literature review provide moderate evidence that probiotic supplements lower blood pressure where baseline BP is borderline HT and supports the growing body of evidence suggesting a potential role for probiotics in reduction of HTN. It is, therefore, recommended that probiotics are used as a complementary therapy to other HTN interventions such as dietary and lifestyle modifications to provide gut and cardiovascular support, particularly where dysbiosis is suspected. Since HTN can be linked to dietary and lifestyle factors, a Nutritional Therapist is well qualified to recommend probiotic supplements as an adjunct to additional personalized dietary/lifestyle interventions to support the cardiovascular system, for example the DASH diet [81], and advise upon incorporation of probiotic/prebiotic food sources to support general gut health. It is anticipated that probiotic supplements may form a short/medium term convenient intervention, whilst a client transitions to an improved diet. Any recommendations would need to be considered in conjunction with a client's medical advice as any consequent BP reduction may require a BP medication review.

Further recommendations

It is evident from this review that further large-scale, longer duration empirical studies using probiotic supplements are required on HT participants to identify most effective strains, dosage, administration as well as duration of any effect. GM analysis at baseline and following intervention would also be useful to establish whether dysbiosis is concurrent with the HTN and the effect of the probiotics on both GM and HTN. This may provide evidence to develop personalized probiotic protocols in the future.

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Conflict of Interest

The authors declare no competing interests.

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