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Effect of a polyphenol-rich dietary supplement containing *Pinus massoniana* bark extract on blood pressure in healthy adults: A parallel, randomized placebo-controlled trial

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ABSTRACT

Objectives: High blood pressure (BP) is a major risk factor for cardiovascular disease and prevalence rates continue to rise with ageing populations. Polypharmacy remains a burden among the ageing, thus alternative effective strategies are warranted. This study investigated the effects of a polyphenols rich dietary supplement containing *Pinus massoniana* bark extract (PMBE) for modulating BP in healthy Australian adults.
Design: This study is a secondary analysis of data from a double-blinded, placebo-controlled clinical trial.
Methods: Sixty-two healthy adults aged 55–75 years were randomized to receive 50 mL dietary supplement containing placebo (0 mg PMBE) or PMBE (1322 mg PMBE) daily for 12 weeks. Seated systolic BP (SBP) and diastolic (DBP) were measured at baseline, 6 weeks and 12 weeks. Effects of PMBE on modulating BP was also explored in this study stratified for SBP status (optimal v high) as well as by SBP medication status. Mixed effect regression modelling was employed involving fixed categorical effects for elapsed time, treatment assignment and their interaction as well as random subject-level intercept to account for within-subject correlations resulting from repeated measurements. Significant models were further examined by addition of covariates and power calculations were performed since this study was a secondary analysis.
Results: SBP significantly reduced (−3.29 mmHg, $p = 0.028$) after PMBE at 12 weeks compared to baseline. SBP in individuals with normal-high SBP (>120 mmHg) in the PMBE group reduced by − 6.46 mmHg ($p = 0.001$) at 12 weeks compared to baseline. No significant changes were reported for individuals with optimal (≤120 mmHg) SBP nor did DBP significantly change in either study groups. In individuals with non-medicated normal-high SBP, SBP significantly reduced by − 7.49 mmHg ($p = 0.001$) and DBP by − 3.06 mmHg ($p = 0.011$) at 12 weeks compared to baseline after PMBE. Cross-group comparisons were not statistically different.
Conclusions: A polyphenol-rich dietary supplement derived from PMBE led to a clinically and statistically significant reduction in SBP in adults. Future studies to investigate the effects of PMBE-polyphenol supplementation on BP are warranted to confirm and explore optimal dose and impact on hypertension.

1. Introduction

Elevated blood pressure (BP) is a major risk factor for heart disease.[1] Over 5 % of the total burden of disease in Australia in 2018 was due to high BP, and this was the 4th leading risk factor contributing to disease burden.[2] Diets high in sodium were the culprit for one-fifth of the high

Abbreviations: ACE, angiotensin I-converting enzyme; BP, blood pressure; CHO, carbohydrates; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DXA, dual-energy x-ray absorptiometry; MDA, malondialdehyde; PAC, proanthocyanidins; PMBE, *Pinus massoniana* bark extract; SBP, systolic blood pressure; SOD, superoxide dismutase.

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BP burden in Australia in 2015, a rate which is higher for men (23 %) than women (17 %).[3] Other factors such as poor diet, excessive alcohol intake, lack of physical activity and obesity increase the risk of high BP.[3] In Australia in 2017–18, the prevalence of uncontrolled high BP rose with increasing age, peaking at 47 % at age 85 years and over.[4] This major health problem presents later in life particularly from 50 years of age due to progressive arterial stiffening as a result of ageing.[5,6] Given Australia's increasing ageing population, with over 27 % (6.8 million) of the total population aged 55 years and over,[7] it is imperative to focus not only on longevity, but increasing quality of life by minimising the development chronic diseases associated with ageing. Current therapeutic strategies involve several lifestyle changes such as weight reduction, dietary intervention with Mediterranean diet/Dietary Approaches to Stop Hypertension (DASH), dietary sodium reduction, increased physical activity, cessation of smoking and moderate/reduction in alcohol intake, often these being the first port of call for managing high BP. In middle-aged to older-aged adults, these strategies may be difficult to adopt and potentially harmful unless carefully supervised by health professionals.[5] Polypharmacy including antihypertensive agents is a common phenomenon in the ageing population, which can lead to drug-related complications and poor pill compliance.[5] Lack of adherence to BP-lowering medication is a key reason for the rise in uncontrolled/poorly controlled hypertension across the globe.[8] Alternative and/or adjunct therapies that are safe and may enhance BP management with the potential to provide a drug alternative for those with moderately high BP are required. Furthermore, this may optimise drug adherence and reduce dose-dependence for those on BP-lowering medication(s).

Proanthocyanidins (PAC) are natural polyphenols widely abundant in fruits, nuts, seeds and red wine.[9] PACs are polymers of flavan-3-ols and are also known as condensed tannins[10,11] with catechin and epicatechin as the key building blocks.[12] PACs have a wide range of protective health benefits such as antioxidant,[13–15] anti-inflammatory,[16,17] anticarcinogenic,[18] antiviral,[13] cardio-protective[19] and hypotensive.[20] PACs are also the main active compounds found in pine bark extracts and are the most abundant compound in various pine species.[21] The French Maritime pine *Pinus pinaster* is the most widely studied in the form of the patented dietary supplement, Pycnogenol®, contains a specific blend, standardised to contain between 65 % and 75 % procyanidins (condensed oligomeric catechin and epicatechin).[22,23] Pycnogenol is currently used as a dietary supplement with therapeutic applications reported for cardiometabolic risk factors, chronic inflammation, circulatory dysfunction, type 2 diabetes and asthma.[23–26] Pycnogenol has also been reported to lower systolic BP (SBP) and diastolic BP (DBP),[27] with increased efficacy when administered concurrently with other treatments.[28] Furthermore, improvements in endothelial function following supplementation with Pycnogenol have been reported in hypertensive individuals.[29] *P. radiata* (trade name, Enzogenol™) is a pine bark extract from 15 to 30 year old New Zealand pine trees and is a richer source of procyanidins than Pycnogenol®.[30] Enzogenol™ is formulated with Vitamin C and has been shown to have antioxidant, anti-inflammatory, anticancer, cardio- and neuroprotective properties[21] and acute hypoglycaemic effects in healthy individuals.[31] *Pinus massoniana* Lamb is another specie of pine native to south and southwest of China. It's bark, pollen, turpentine and needles have been used in traditional Chinese medicine for the treatment of rheumatic arthralgia, hypertension, neurasthenia and chilblain.[32,33] In preclinical studies, *Pinus massoniana* bark extract (PMBE) has been reported to inhibit migration of cancer cells,[34] inhibit growth of human breast cancer cells[35] and reduce oxidative stress.[36] Most reports on PMBE are preclinical and thus focus on the cellular level. Overall, the efficacy or safety of pine bark extract supplements remains inconclusive, with current human studies being small in sample size, limited in RCT study design per health condition, variation in outcome measures with poor quality in reporting.[37] Clinical data for recommending the appropriate dose, regime and formulation are lacking and required to uncover the potential health benefits of PMBE and PACs derived from PMBE. There are currently no human studies demonstrating the effect of PACs derived from PMBE on modulating BP, nor are there any studies investigating the physiological effects of a dietary supplement containing PMBE.

The present study aims to evaluate the effects of a dietary supplement rich in PACs derived from PMBE on systolic and diastolic BP in healthy adults. This pilot study is a secondary analysis of an existing study exploring the effects of PMBE on oxidative stress. Findings from the current study could provide novel insight into the potential blood-pressure modulating effects of a dietary supplement rich in PACs from PMBE and may inform the conduct of future human clinical trials to specifically investigate the antihypertensive effects of PMBE.

2. Methods

2.1. Recruitment

Participants were recruited from the Hunter region (NSW, Australia) via notice board flyers placed around the local community, word of mouth, media outlets (radio announcements and newspaper articles), and subjects who participated in earlier studies at our research facility were also invited to participate. Volunteers were assessed for eligibility over the phone or in person and were eligible if they were: healthy adults aged 55–75 years old. Volunteers were excluded if they had/were: a diagnosed chronic disease such as CVD, diabetes mellitus, renal or hepatic condition, neurological condition, autoimmune condition; diagnosed chronic inflammatory condition; a history of gastrointestinal disorders; currently taking medications known to influence the study outcomes e.g., non-steroidal anti-inflammatory medications; routinely taking supplements known to influence the study outcomes e.g., curcumin, coenzyme Q10 or Vitamin E; taking anticoagulant medications; current smokers or smoked in the past 6 months; currently participating in another diet/lifestyle intervention study; made significant changes to diet/lifestyle in the past 3 months; an excessive alcohol consumer (>10 standard drinks per week[38]); > 5 % body weight loss in the past 6 months; BMI $\geq$ 40 kg/m^2; and allergic/intolerant to fig, kiwifruit or papaya. Eligible volunteers were provided with a detailed description of the study and written informed consent was mandatory for enrolment in the study. The study protocol was approved by the Human Research Ethics Committee, University of Newcastle (H-2020–0271) and all procedures were conducted in accordance with the 1975 Declaration of Helsinki as revised in 2013. The trial was registered with the Australian New Zealand Clinical Trials Registry at https://www.anzctr.org.au/ (ACTRN 12621000190808).

2.2. Study design

This study was a 12-week, double-blinded, randomised, placebo-controlled trial with two parallel groups. Intervention groups were allocated using a computer-generated permuted block randomisation method and participants were stratified by sex (Random Allocation Software version 1.0.0). As part of their habitual diet/lifestyle, participants were randomly allocated in a 1:1 ratio to consume one of the following every day for 12 weeks: 50 mL liquid drink containing either placebo (0 mg *Pinus massoniana*, providing 32 mg total polyphenols) or PMBE (1322 mg of *Pinus massoniana*, providing 432 mg total polyphenols). The PMBE product is commercially available as *RecoveR8* (Tismor Health & Wellness Pty Ltd, NSW). Each daily portion of liquid provided 43.7 mL purified water, 2938.5 mg inulin, 1322 mg Pinus massoniana, 734.5 mg glycerin, 489.5 mg papain enzyme (derived from papaya), 171.5 mg xanthum gum, 150 mg citric acid anhydrous, 98 mg Actinidia chinensis (derived from kiwifruit), 73.5 mg cranberry extract, 73.5 mg cranberry flavour and 49 mg pomegranate dry extract as the key ingredients. The placebo liquid was mainly purified water with inulin, microcrystalline cellulose and small amounts of flavourings. It was devoid of *Pinus massoniana* and any other fruit extracts. Tismor

Health & Wellness (Kingsgrove, NSW Australia) were responsible for manufacturing and packaging the placebo and PMBE products. To ensure double-blinding, supplement bottles and storage boxes were labelled with colour-coded stickers upon packaging by the manufacturer. Participants were de-identified and assigned number codes. The placebo and PMBE liquids were identical in sensory characteristics. Compositional analyses of placebo and PMBE products were conducted by an independent laboratory (Analytical Research Laboratory, Southern Cross University, Lismore, NSW, Australia). Total PACs and total polyphenolics were identified via UV spectroscopy and total catechins, total anthocyanins and procyanidins were identified through high-performance liquid chromatography and procyanidins (Table 1). Participants were instructed to consume the entire supplement each day with breakfast as part of their usual dietary pattern. Compliance was monitored by evaluation of the supplement consumption log, empty vs full supplement bottle count-back and analysis of habitual dietary intake before-during-after intervention period.

2.3. Clinical assessments

Participants attended Nutraceuticals Research Program's clinical trial facility at the University of Newcastle (Callaghan, NSW Australia) after an overnight fast (10 h) at baseline (0 weeks), mid-way (6 weeks) and post-intervention (12 weeks). BP, anthropometric measures, medical history, habitual dietary intake and physical activity patterns were collected. Body composition including bone mineral density and bone mineral content was collected at the Newcastle Bone Density Centre (Waratah, NSW Australia) which is a private medical imaging centre.

2.4. Blood pressure

BP was measured in the fasted state (overnight, 10 h) in the seated position using a digital sphygmomanometer (Microlife®, BP3AD1-A Heerbrugg, Switzerland). Three serial measurements with 1-minute rest in between of systolic BP (SBP) and diastolic BP (DBP) were taken in the supported left arm of a rested participant (5–10 min). The arm was positioned at the same height as the heart and feet supported on the ground or stool. The first measurement was discarded and an average of the remaining two were considered as the final measurement. Participants refrained from alcohol consumption and vigorous physical activity for 24 h prior to their appointments.

2.5. Anthropometry

Height was measured using a wall-mounted stadiometer with a movable head piece (Seca 206 Bodymeter Wall Height Measure Ruler). Waist circumference was measured using a tensible tape measure positioned midway between the lower rib margin and the iliac crest horizontally (approximately in line with the navel) on bare skin. Height (cm), waist circumference (cm) and weight (kg) were collected to the nearest 0.1 units in light clothing without shoes.

Dual total body scans were conducted using dual-energy x-ray absorptiometry (DXA) (GE Lunar Prodigy Pro Bone Mineral Densitometer, Medtel, Madison WI and GE Healthcare software version 2017) by a qualified technician. All participants were required to complete a DXA Screening Questionnaire before the scan. Participants were wearing only a light clinical gown and underwear to which they then lay on a scanner bed and manual adjustments were made to ensure the regions of the body were contained within the set parameters while a scanning arm passed over the body. The DXA scan took approximately 6 min to complete. The scanner provided percentage total and regional body fat and muscle mass. Absolute total bone mineral density and bone mineral content was also provided by the scan.

Table 1
Composition of study products.[1].

	Placebo (mg/day)	PMBE (mg/day)
Polyphenolics (CE)	32.0	431.5
Total catechins	2	29.5
Total PACs	10.5	59.5
Total anthocyanosides	nd	0.25

[1] Composition is reported for mg per daily dose (50 mL) of study product. Composition was quantified by The Analytical Research Laboratory at Southern Cross University.
CE, catechin equivalents; nd, not detected; PACs, proanthoycanidins.

2.6. Medical history, dietary intake and physical activity

A self-administered medical and demographic history questionnaire was completed by all participants at baseline to collect information regarding past and present medical conditions; history of blood lipid profile, prescribed or over-the-counter medication(s), habitual supplement use and habitual consumption of alcohol and smoking status. Habitual diet and physical activity patterns at baseline and post-intervention were assessed by a 3-day food diary and physical activity questionnaire (International Physical Activity Questionnaire; IPAQ Long Last 7 Days Self-Administered Format, October 2002), respectively. Dietary data was evaluated using FoodWorks, Xyris®, Professional Edition Version 10.0.4266. Physical activity data was interpreted as metabolic equivalent of task minutes per week (MET/week) to measure the energy cost of usual physical activities.

2.7. Statistical analysis and sample size determination

This study is a secondary analysis of a previous study[39] which aimed to investigate the effects of PMBE on malondialdehyde (MDA) concentrations. In the original study, sample size was determined based on previous estimates of variance in MDA concentrations in healthy adults (Mean = 3.72, SD ± 0.7)[40] to elicit 80 % power at a significance level of 0.05 to detect a 0.65 nmol/mL (~17 %) difference between the placebo and PMBE group, a total of 50 participants (n = 25 per group) was required. To account for a potential 20 % dropout rate, a total of 60 (n = 30 per group) participants were recruited.[39] Data were assessed for normality using the Shapiro-Wilk test and visual plots such as histograms and box plots. Quantitative variables were summarised using mean ± SEM or median and interquartile range depending on normality. Qualitative variables were summarized by frequencies and percentages. An independent samples t-test was used to compare mean baseline characteristics across groups of SBP status for normally distributed data and Mann-Whitney U test was used for non-normally distributed data. The χ^2 test was used to compare the distribution of categorical variables across groups. Mean (SEM) change in BP and other outcome measures from baseline to 6 weeks and overall (12 weeks) were summarised by placebo and PMBE group. Participants were stratified based on SBP status at baseline: optimal $\leq$ 120 mmHg and normal to high SBP $>$ 120 mmHg based on the National Heart Foundation classification of clinic BP in adults for comparisons.[35] The two SBP groups will be referred to as 'optimal SBP' and 'high SBP' in this paper. Further statistical exploration included stratification of participants who were medicated vs not medicated for BP.

An exploratory mixed effect regression model was used to evaluate the mean change in participant's BP concentrations. The model included fixed categorical effects for elapsed time, treatment assignment and their interaction as well as random subject-level intercept to account for within-subject correlations resulting from repeated measurements on the same participants at baseline, 6 weeks and 12 weeks. The same analyses were performed for body composition and physical activity levels. If models were found to be significant for change in response variables across groups, variables such as age and BMI were included in the model to examine the potential effect of confounding. Regarding model fit, linearity and normality were assessed by graphical inspection

of residuals and fitted values. Since this is a secondary analysis, power calculations were performed for any statistically significant findings for BP to assess the probability of rejecting the null hypothesis that the change in BP in the intervention groups is zero.

All tests were two-tailed at the level of significance of 0.05 and all data was analysed using StataCorp 2015 *Release 14*. (College Station, TX: StataCorp LP).

3. Results

3.1. Baseline characteristics

Sixty-two participants were recruited during the period March 2021 to mid-October 2021. Two participants dropped out of the trial due to undisclosed personal reasons (n = 1) and bodily pain (n = 1). Due to NSW Health Government restrictions in response to the COVID-19 pandemic, a lockdown in the Hunter area occurred between early-August to early-October which resulted in incomplete data collection for eight participants in both the placebo group and PMBE group who were due 6-week follow-up timepoint. A further one participant from the placebo group and two participants from the PMBE group had incomplete data collected at 12-weeks. A total of 60 participants completed the trial and all available data from participants randomized from baseline were included in the final analysis (n = 62). At baseline, 20 participants had optimal and 42 had high SBP (Fig. 1). Nearly all the males in this study had high SBP at baseline in both groups and this proportion compared to females was significantly apparent (Table 2). Majority of participants were Oceanian (Australian) and ethnicity did not differ between groups or by SBP status. Individuals with high SBP tended to be older in both groups and individuals with high SBP in the PMBE group were significantly taller than those with optimal SBP. Nine people in this study were taking medications for high BP all of which had high SBP at baseline (n = 4 in placebo group and n = 5 in PMBE group). Overall medication usage was not different across groups or SBP status.

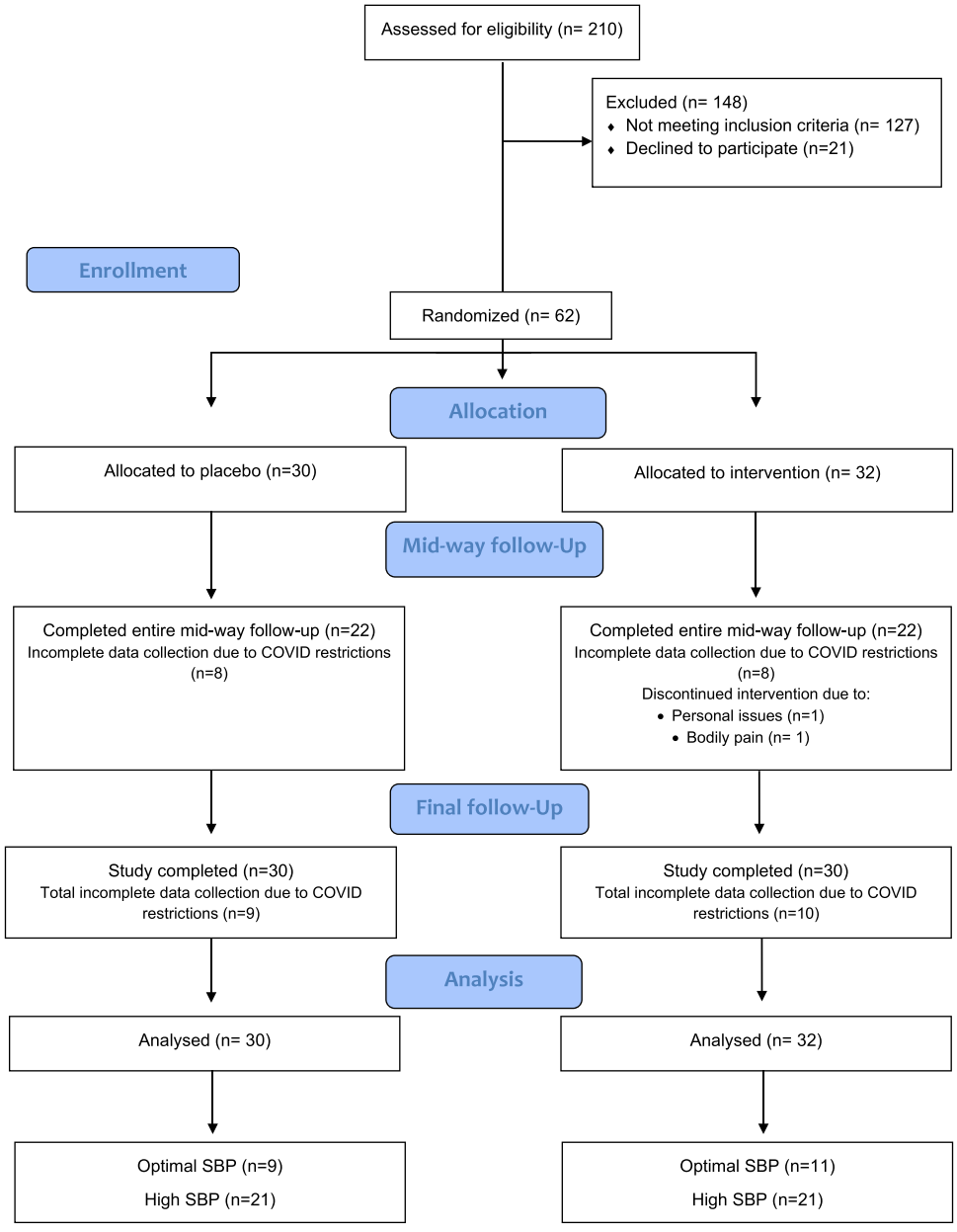

Fig. 1. CONSORT schematic of participant recruitment, screening and assessment.

Table 2
Participant characteristics at baseline in the placebo and PMBE groups by SBP status at baseline[1].

	Placebo (n = 30)			PMBE (n = 32)		
	Normal SBP (n = 9)	High SBP (n = 21)	P^2	Normal SBP (n = 11)	High SBP (n = 21)	P^2
Sex, *n* (%)			0.034			0.009
Male	1 (8.3)	11 (91.7)		1 (7.7)	12 (92.3)	
Female	8 (44.4)	10 (55.6)		10 (52.6)	9 (47.4)	
Ethnicity, *n* (%)			0.099			0.086
Oceanian	4 (23.5)	13 (76.5)		3 (20)	12 (80)	
Oceanian/ North-west European	4 (80)	1 (20)		1 (16.7)	5 (83.3)	
North-west European	1 (20)	4 (80)		6 (66.7)	3 (33.3)	
South-east European	0 (0)	1 (100)		0 (0)	0 (0)	
Other[3]	0 (0)	2 (100)		1 (50)	1 (50)	
Age (y)	61.7 ± 1.11	64.8 ± 1.2	0.122	63.6 ± 1.1	66.1 ± 1.2	0.197
Height (cm)	167.9 ± 1.8	166.5 ± 2.3	0.707	161.2 ± 1.8	169.6 ± 2.3	0.021
Medication use for, *n* (%):						
High BP	0 (0)	4 (100)	0.160	0 (0)	5 (100)	0.078
High cholesterol	0 (0)	1 (100)	0.506	2 (40)	3 (60)	0.773
Gastroesophageal reflux disease	1 (50)	1 (50)	0.523	0 (0)	4 (100)	0.122
Anxiety	2 (50)	2 (50)	0.348	0 (0)	1 (100)	0.462
Other[4]	4 (50)	4 (50)	0.149	2 (40)	3 (60)	0.773
Compliance[5]	99.2 ± 0.3	98.7 ± 0.73	0.658	99.3 ± 0.3	98.3 ± 0.4	0.123

[1] Values are reported as means ± SEM. for continuous measures and as n (%) for categorical measures. Normal SBP is individuals with SBP ≤ 120 mmHg at baseline and high SBP is individuals with SBP > 120 mm Hg at baseline.
[2] Categorical data compared using Pearson chi square test and continuous data compared using independent samples t-test
[3] Other races include South-East Asian (n = 1), Oceanian/Southern & Eastern European (n = 1), North-West European/North African & Middle Eastern (n = 1) and North African & Middle Eastern / Sub-Saharan African (n = 1).
[4] Values reported as median and (interquartile range) as data is non-normally distributed.
[5] Other includes medications for hypothyroidism, herpes, hormone replacement.
[6] Compliance is reported for all 60 participants who completed the 12-week intervention.
BP, blood pressure; PB, pine bark; PL, placebo; SBP, systolic blood pressure

3.2. Nutrient intake and compliance

Nutrient intake was similar at baseline and post-intervention within study groups and between SBP status (Supplementary Table 1). No statistically significant changes in nutrient intake from baseline to post-intervention within groups was reported nor were there any differences in nutrient intake between SBP status groups at baseline or post-intervention. Mean change in nutrient intake parameters at baseline or post-intervention did not statistically significantly differ across groups. The study supplement was well tolerated by all participants with excellent compliance overall (98.7 ± 2.3 %) which was comparable across study groups and SBP status (Table 2).

3.3. Anthropometry and physical activity

In the PMBE group, waist circumference was significantly lower in individuals with optimal SBP at baseline and post-intervention compared to individuals with high SBP (Table 3). Waist-to-hip ratio was significantly higher in individuals with high SBP compared to optimal SBP at every timepoint in the PMBE group. The same was only evident at 6 weeks in the placebo group. Mean body weight was significantly higher at every timepoint in individuals with high SBP compared to optimal SBP in the PMBE group (Table 3). Body weight significantly increased by 0.65 kg from baseline to post-intervention in individuals with high SBP in the placebo group. Conversely, the same occurred in individuals with optimal SBP in the PMBE group (+0.69 kg). BMI was significantly higher at 6 weeks in individuals with high SBP compared to optimal SBP in both groups, and this trend was also evident post-intervention in the PMBE group. Lean muscle mass significantly increased from baseline to 6 weeks by 0.52 kg in individuals with optimal SBP in the PMBE group, and from baseline to post-intervention by 0.71 kg in individuals with high SBP in the placebo group. However, mean lean muscle mass was significantly higher at each timepoint in individuals with high SBP compared to optimal SBP in the PMBE group. Physical activity did not significantly alter within groups by SBP status across study timepoints, nor did change in physical activity levels differ across groups by SBP status at any timepoints (Table 3).

3.4. Systolic and diastolic BP by intervention groups

SBP significantly reduced (−3.29 mmHg, $p = 0.028$) in the PMBE group post-intervention compared to baseline (Table 4). Power calculation revealed 0.556 probability (power) of correctly rejecting the null hypothesis in the PMBE group given n = 28 pairs of participants, a Type I error probability α of 0.05 and a true difference in population means of SBP from baseline to post-intervention of − 3.29 mmHg and standard deviation of 7.93 mmHg. The mean change in SBP was not statistically significantly different between the PMBE and placebo group at any timepoint, nor did SBP change in the placebo group over time. DBP did not significantly change within either group and nor was mean change in DBP significantly different across groups at any timepoint.

3.5. Systolic and diastolic BP by SBP status

Mean SBP at each timepoint was significantly different between individuals with optimal SBP vs high SBP within each study group (Table 5). In individuals with high SBP, SBP significantly reduced by − 6.46 mmHg ($p = 0.001$) in the PMBE group post-intervention compared to baseline (Fig. 2**B**). Power calculation revealed 0.866 probability (power) of correctly rejecting the null hypothesis given n = 19 pairs of participants with high SBP in the PMBE group, a Type I error probability α of 0.05 and a true difference in population means of SBP from baseline to post-intervention of − 6.46 mmHg and standard deviation of 8.69 mmHg. The mean change in SBP was not statistically significantly different between the PMBE and placebo group at any timepoint, nor did SBP change in the placebo group over time.

In individuals with optimal SBP at baseline, SBP did not significantly change at any timepoint within- or across groups (Fig. 2A). Mean DBP was significantly different at each timepoint between those with optimal vs high SBP status in the PMBE group (Table 5). The same was reported for the placebo group except for at 6 weeks whereby the mean DBP did not significantly differ between individuals with optimal vs high SBP status. Mean change in DBP was not statistically significant within or across groups for intervention or SBP status (Fig. 2C and 2D**)**.

Table 3
Anthropometry, body composition and physical activity levels at baseline, 6 weeks and 12 weeks in placebo and PMBE groups by SBP status.

	Optimal SBP (≤120 mmHg)			High SBP (>120 mmHg)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Waist (cm)						
Placebo	86.89 (2.64)	85.15 (3.74)	87.28 (3.49)	93.25 (2.24)	93.33 (2.32)	94.33 (2.65)
n[1]	9	5	9	21	17	20
Δ[2]			0.39 (1.12)			1.12 (54)
PMBE	85.00 (4.05)[a]	85.02 (4.53)	83.83 (3.86)[b]	95.74 (2.27)[a]	94.24 (2.39)	94.89 (2.27)[b]
n	11	8	9	21	14	19
Δ	–	–	0.64 (0.53)	–	–	0.08 (0.59)
WHR						
Placebo	0.85 (0.04)	0.82 (0.04)[c]	0.82 (0.05)	1.05 (0.06)	1.07 (0.07)[c]	1.06 (0.07)
n	9	9	9	21	20	21
Δ	–	–	-0.03 (0.04)	–	–	0.006 (0.02)
PMBE	0.85 (0.09)[d]	0.86 (0.09)[e]	0.86 (0.09)[f]	1.11 (0.05)[d]	1.10 (0.05)[e]	1.09 (0.05)[f]
n	11	9	10	21	20	20
Δ	–	–	0.04 (0.02)	–	–	-0.009 (0.02)
Weight (kg)						
Placebo	67.79 (3.35)	66.70 (3.14)	67.78 (3.81)	73.10 (3.04)	73.97 (3.34)	73.75 (3.14)
n	9	9	9	20	21	21
Δ	–	–	-0.01 (0.90)	–	–	0.65 (0.24)*
PMBE	61.94 (3.92)[g]	59.96 (3.89)[h]	60.31 (3.37)[i]	75.49 (3.06)[g]	74.36 (2.97)[h]	74.55 (2.98)[i]
n	11	9	10	21	20	20
Δ	–	–	0.69 (0.23)*	–	–	0.27 (0.37)
BMI (kg/m^2)						
Placebo	23.74 (0.93)	23.31 (0.93)[j]	23.58 (1.07)	26.00 (0.69)	26.38 (0.71)[j]	26.17 (0.71)
n	9	9	9	21	20	21
Δ	–	–	-0.17 (0.30)	–	–	0.16 (0.10)
PMBE	23.57 (1.34)	22.98 (1.28)[j]	22.97 (1.08)[k]	25.83 (0.52)	25.62 (0.53)[j]	25.64 (0.54)[k]
n	11	9	10	21	20	20
Δ	–	–	0.28 (0.13)	–	–	0.02 (0.16)
% body fat						
Placebo	35.41 (2.52)	34.56 (2.66)	34.97 (2.26)	33.72 (1.97)	33.53 (1.98)	33.22 (2.00)
n	9	9	9	21	20	21
Δ	–	–	-0.44 (0.73)	–	–	-0.50 (0.26)
PMBE	33.17 (2.91)	31.86 (2.76)	31.42 (2.32)	33.31 (1.43)	33.07 (1.49)	33.11 (1.46)
n	11	9	10	21	20	20
Δ	–	–	0.08 (0.37)	–	–	-0.17 (0.28)
LMM (kg)						
Placebo	41.94 (1.99)	41.70 (1.60)	42.21 (2.13)	46.81 (2.50)	47.54 (2.66)	47.53 (2.51)
n	9	9	9	21	20	21
Δ	–	–	0.28 (0.30)	–	–	0.71 (0.19)**
PMBE	39.12 (1.78)[l]	38.95 (2.23)[m]	39.54 (2.00)[n]	48.67 (2.34)[l]	48.07 (2.29)[m]	48.20 (2.30)[n]
n	11	9	10	21	20	20
Δ	–	–	0.52 (0.22)*	–	–	0.28 (0.17)
METS (mins/wk)						
Placebo	5190 (4386, 6744)	4405 (3401, 4946)	5369 (4014, 7998)	3261 (2343, 6012)	3180 (1898, 5595)	3437 (1573, 6675)
n	9	9	9	21	21	21
Δ	–	–	309 (976)	–	–	122 (684)
PMBE	3945 (2574, 9372)	4107 (3798, 6402)	3579 (2610, 6132)	3715 (1941, 7224)	3701 (1617, 6284)	4581 (2970, 6438)
n	11	10	10	21	21	19
Δ	–	–	-1057 (1421)	–	–	503 (850)

Data is presented as mean (SEM) and mean (95 % CI). Paired samples t-test was used for within group comparisons from baseline to post-intervention and Independent samples t-test was used to examine differences in mean values across groups at each timepoint. Values in the same row with a common superscript letter significantly differ: a $p < 0.05$, b $p < 0.05$, c $p < 0.05$, d $p < 0.05$, e $p < 0.05$, f $p < 0.05$, g $p < 0.05$, h $p < 0.01$, i $p < 0.01$, j $p < 0.05$, k $p < 0.05$, l $p < 0.05$, m $p < 0.05$, n $p < 0.05$.

[1] *n,* number of participants with available data

LMM, lean muscle mass; MET, metabolic equivalents; PMBE, *Pinus massoniana* bark extract; SBP, systolic blood pressure.

3.6. Change in systolic and diastolic BP in individuals with high SBP who were/were not medicated for high BP

Majority of individuals with high SBP were not medicated for high BP in both groups (80.9 % in placebo group and 76.2 % in PMBE group). In the PMBE group, SBP significantly reduced by − 7.49 mmHg ($p = 0.001$) and DBP by − 3.06 mmHg ($p = 0.011$) in individuals with non-medicated high SBP at 12 weeks compared to baseline (Table 6). The mean change in SBP was not statistically different between the PMBE and placebo group at any timepoint, nor did SBP change in the placebo group over time. Power calculation revealed 0.842 probability (power) of correctly rejecting the null hypothesis in the PMBE group given n = 14 pairs of participants, a Type I error probability α of 0.05 and a true difference in population means of SBP from baseline to post-intervention of − 7.49 mmHg and standard deviation of 8.75 mmHg. Power calculation revealed 0.644 probability (power) of correctly rejecting the null hypothesis in the PMBE group given n = 14 pairs of participants, a Type I error probability α of 0.05 and a true difference in population means of DBP from baseline to post-intervention of − 3.06 mmHg and standard deviation of 4.51 mmHg.

4. Discussion

This is the first human study to demonstrate a blood-pressure lowering effect of a polyphenol-rich dietary supplement containing PACs derived from a combination of plant bioactives including PMBE in

Table 4
Change in systolic and diastolic BP in the placebo group and PMBE group from baseline, 6-weeks and 12-weeks (post-intervention).[a].

	Time					Change	
	Baseline	6-weeks	n	12-weeks	n	Δ 1 (95 % CI)[b]	Δ 2 (95 % CI)[c]
SBP (mmHg)							
Placebo	125.95 (2.90)	128.05 (3.12)	22	124.21 (3.25)	29	0.09 (−3.55, 3.72)	-1.18 (−4.87, 2.52)
PMBE	125.19 (2.89)	121.68 (2.89)	22	122.86 (2.52)	28	-1.34 (−3.90, 1.23)	-3.29 (−6.23, −0.35)*
Difference[d]						-1.42 (−5.88, 3.03)	-2.11 (−6.83, 2.60)
DBP (mmHg)							
Placebo	77.87 (1.78)	79.77 (2.14)	22	76.83 (1.70)	29	0.48 (−2.28, 3.24)	-0.63 (−2.20, 0.94)
PMBE	75.0 (1.94)	71.52 (1.53)	22	73.59 (1.77)	28	-0.87 (−2.33, 0.60)	-1.35 (−3.17, 0.47)
Difference						-1.34 (−4.47, 1.78)	-0.72 (−3.13, 1.69)

DBP, diastolic blood pressure; PMBE, *Pinus massoniana* bark extract; SBP, systolic blood pressure.

[a] Baseline data is for all participants who commenced the trial (n = 30 placebo, n = 32 active). Data at 6 and 12 weeks is presented for all participants unless otherwise specified in respective table columns and presented as mean (SEM) or median. Mixed models were used to examine the effect of time within treatment groups as well as the interaction between time and treatment across groups. Data for mixed models is presented as mean estimates (95 % confidence intervals). All data presented is for adjusted models only using pre-specified variables. Significant findings are indicated as $*p < 0.05$

[b] Effect of time within treatment group from baseline to 6 weeks

[c] Effect of time within treatment group from baseline to 12 weeks (post-intervention)

[d] Interaction between time x treatment is presented as intervention minus control.

Table 5
Mean systolic and diastolic BP at baseline, 6 weeks and 12 weeks in placebo and PMBE groups by SBP status.

	Optimal SBP (≤120 mmHg)			High SBP (>120 mmHg)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
SBP (mmHg)						
Placebo	106.72 (2.32)[a]	109.40 (4.18)[b]	109.17 (3.89)[c]	134.19 (2.28)[a]	133.53 (2.65)[b]	130.98 (3.46)[c]
n[1]	9	5	9	21	17	20
PMBE	107.09 (2.04)[d]	108.63 (2.18)[e]	111.06 (2.87)[f]	134.67 (2.36)[dg]	129.14 (2.82)[e]	128.45 (2.63)[fg]
n	11	8	9	21	14	19
Difference[2]	–	0.91 (−5.26, 7.07)	1.12 (−4.22, 6.46)	–	-2.55 (−8.52, 3.42)	-3.54 (−9.006, 1.93)
DBP (mmHg)						
Placebo	69.61 (1.82)[h]	72.60 (3.60)	70.22 (1.61)[i]	81.40 (1.97)[h]	81.88 (2.37)	79.80 (2.04)[i]
n	9	5	9	21	17	20
PMBE	66.27 (1.71)[j]	66.63 (1.41)[k]	66.56 (1.53)[l]	79.57 (2.26)[j]	74.32 (1.91)[k]	76.92 (2.12)[l]
n	11	8	9	21	14	19
Difference	–	-2.45 (−7.90, 2.99)	-0.11 (−4.87, 4.65)	–	-1.09 (−4.48, 2.28)	-0.93 (−4.02, 2.16)

Baseline data is for all participants who commenced the trial (n = 30 placebo, n = 32 intervention) and data at 6 and 12 weeks is presented for all participants unless otherwise specified in respective table columns. Data is presented as mean (SEM) and mean (95 % CI). Independent samples t-test was used to examine differences in mean SBP across groups at each timepoint. Values in the same row with a common superscript letter significantly differ: a $p < 0.0001$, b $p < 0.001$, c $p < 0.001$, d $p < 0.0001$, e $p < 0.001$, f $p < 0.001$, g $p < 0.01$, h $p < 0.01$, i $p < 0.01$, j $p < 0.001$, k $p < 0.05$, l $p < 0.01$

[1] *n,* number of participants

[2] Mixed models were used to examine the effect of time within treatment groups as well as the interaction between time and treatment across groups (difference). Data is presented is for adjusted models only using pre-specified variables (BMI and age) and data is presented as mean estimates (95 % confidence intervals). Statistical significance indicated by ** $p = 0.001$.

DBP, diastolic blood pressure; PMBE, *Pinus massoniana* bark extract; SBP, systolic blood pressure.

healthy Australian adults. This secondary analysis prompts further exploration into the clinically relevant reduction (−6.46 mmHg) in SBP reported in individuals with moderately high SBP at baseline following 12 weeks PMBE supplementation. A 5 mmHg reduction in SBP following pharmacological treatments has been shown to reflect a 10 % reduced risk of major cardiovascular events, irrespective of previous diagnoses of CVD.[41] This risk reduction is apparent even in those with normal or normal-high BP values, representing the status of the majority of participants in this study. Future studies powered to examine the BP modulating effects of PACs derived from PMBE are warranted to delineate the dose response, duration, and interplay with pharmacological interventions for optimising BP management and cardio-protection in humans.

The average SBP of individuals at baseline in this study is similar to that of the Australian population in the same age group, whereby two thirds of participants in this trial had moderately high SBP.[42] Like the Australian population, males in this study had significantly higher baseline SBP compared to females and the proportion of males was evenly distributed when groups were stratified by SBP status. Thus, findings from this study can be generalised to the Australian population aged between 55 and 75 years for BP management.

Dietary polyphenols have been proposed to alleviate hypertension and reduce BP via mechanisms such as reducing expression of nuclear factor-kB (NF-κB) mediated inflammatory cytokines; reducing oxidative stress by improving enzymatic activities of superoxide dismutase (SOD), catalase and glutathione peroxidase and reducing lipid peroxidation; and activating redox-sensitive phosphoinositide 3-kinase/Akt pathway, resulting in elevated formation of nitric oxide.[43] Clinical trials evaluating the combinations of plant bioactives used in the supplement of the current study are rare, however, polyphenols from food sources such as grapes, resveratrol (red wine), olive oil, cocoa and green tea have been evaluated and at various dosages. A systematic review and meta-analysis of 10 trials reported a significant reduction in SBP by 1.48 mmHg in grape-polyphenol supplemented subjects compared to control subjects.[44] Notably, supplementation with a polyphenol-rich olive oil (30 mg total polyphenols per day) led to a significant 7.91 mmHg reduction in SBP and 6.65 mmHg reduction in DBP after 2 months compared to a polyphenol-free olive oil in women with normal-high BP or stage 1 hypertension.[45] Polyphenols derived from a blend of plant bioactives such as grape seed and skin, green tea, resveratrol, quercetin,

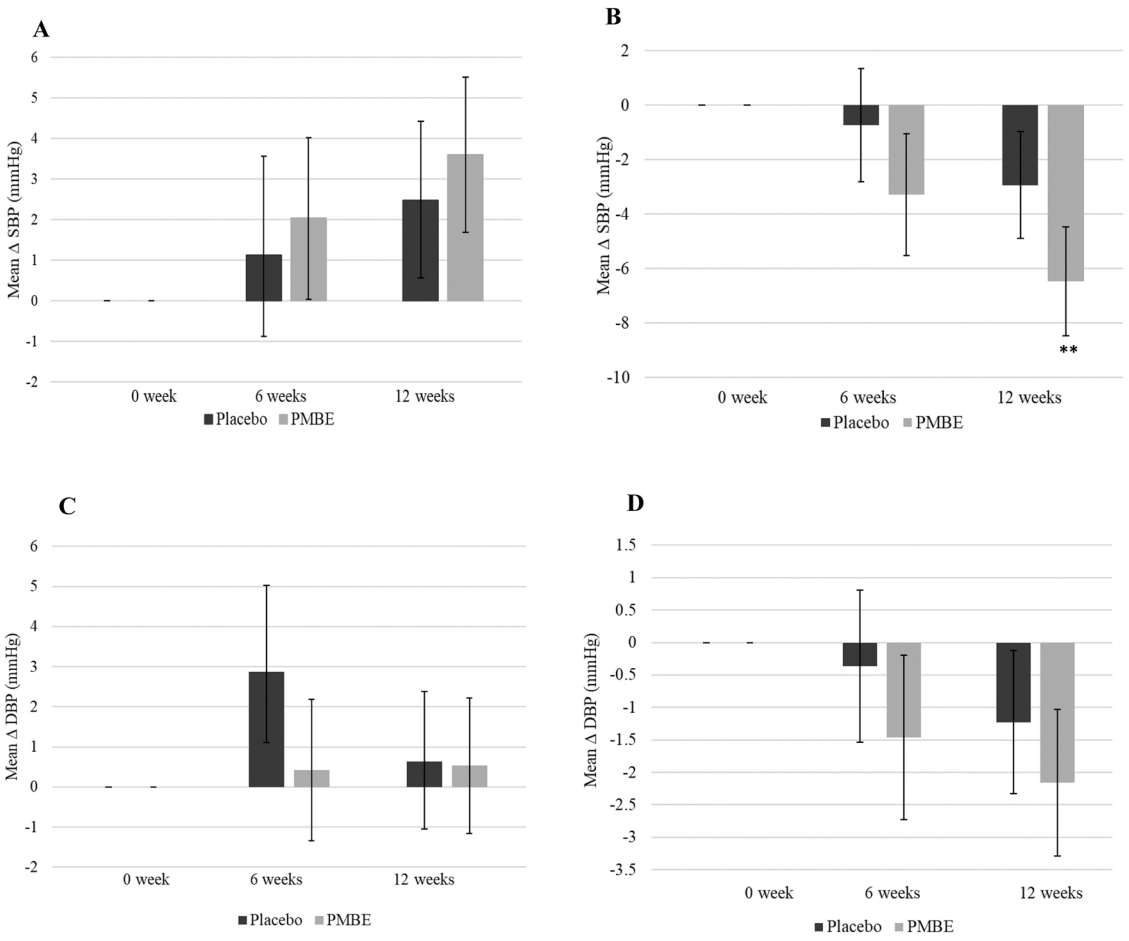

Fig. 2. Mean change in SBP and DBP (with standard error bars) over time in the placebo and PMBE groups by SBP status. Mixed models were used to examine the effect of time within treatment groups as well as the interaction between time and treatment across groups (difference). Data presented is for adjusted models only using pre-specified variables (BMI and age) and data is presented as mean estimates (95 % confidence intervals). A, mean change in SBP in individuals with optimal SBP in the PMBE group and placebo group. B, mean change in SBP in individuals with high SBP in the PMBE group and placebo group. C, mean change in DBP in individuals with optimal SBP in the PMBE group and placebo group. D, mean change in DBP in individuals with high SBP in the PMBE group and placebo group. Statistically significant change from baseline ** $p = 0.001$.

Ginkgo biloba and bilberry supplemented in the form of capsules in hypertensive individuals led to a significant reduction in DBP with no changes in SBP after 4 weeks.[46] The total polyphenolic content of this plant bioactive supplement blend was not reported, however, combined extract content totalled 550 mg/day. Rostami et al. conducted an 8-week RCT on individuals with type 2 diabetes and demonstrated a significant and comparable reduction in SBP (−5.93 mmHg) and DBP (−6.4 mmHg) following 25 g/day polyphenol-rich dark chocolate compared to white chocolate.[47] The daily total polyphenolic content provided in this study was 450 mg/day which is comparable to that of the current study (432 mg/day) and could explain the similar magnitude of SBP-lowering achieved in the current study. Likewise, Almoosawi et al. reported slightly lower reductions in SBP and DBP in overweight females supplemented dark chocolate containing 500 mg of polyphenols daily for 4 weeks.[48] Future studies are warranted to confirm the adequate dose of polyphenols as well as influence of polyphenol source, however, from previous studies and the current study, a supplemental dose of ~450–500 mg/day appears to have clinically relevant BP-lowering effects.

A systematic review and meta-analysis of RCTs summarising the BP-lowering effects of the well-established DASH diet compared to control revealed a pooled reduction in SBP compared to control diets in individuals with moderately elevated SBP.[49] The use of PMBE supplement in the current study led to a comparable reduction in SBP, however, was statistically non-significant. Our study findings suggest the potential use of PMBE as an adjunct or alternative to existing dietary strategies for enhancing the BP-lowering capacity of non-pharmacological therapies. The therapeutic benefits attributed to the PMBE dietary supplement is likely due to the rich polyphenolic content, delivering 432 mg total polyphenols of which 59.5 mg were PAC per daily dose. A systematic review and meta-analysis of six human RCTs (10 treatment arms) across 376 healthy, pre-hypertensive and mildly hypertensive subjects reported significant reductions in pooled SBP, DBP and arterial pressure following supplementation with PACs.[20] Reductions in SBP were significantly lower in trials conducted < 12 weeks compared to 12–16 weeks. The SBP-lowering effect is much lower than reported in the current study (−4.6 mmHg vs −6.5 mmHg respectively), however, higher dosages of PACs ranging from 100 to 400 mg/day were administered across the included studies. All six trials administered supplementation via tablets/capsules, four of which derived PACs from grape seeds/extract, one from French maritime pine bark and the other Acacia bark extract. Therefore, potential formulation variability, delivery and derivation of PACs could impact their SBP-lowering efficacy. The PACs in the current study were delivered as part of a formulation in combination with other food bioactives. The potential synergy between food bioactives and administration via a liquid with a meal, may as a delivery mode enhance absorption and bioavailability of PACs and the other polyphenolic components; potentially leading to the greater efficacy in SBP-lowering reported compared to previous studies. Moreover, the participants in this study were advised to take the PMBE supplement

Table 6
Change in systolic and diastolic blood pressure in the placebo group and PMBE group from baseline, 6-weeks and 12-weeks (post-intervention) in individuals with high systolic blood pressure at baseline by BP medication status.[1].

	Time						Change	
Medicated for high blood pressure								
	Baseline	**n**	**6-weeks**	**n**	**12-weeks**	**n**	**Δ 1 (95 % CI)[2]**	**Δ 2 (95 % CI)[3]**
SBP (mmHg)								
Placebo	128.88 (3.19)	4	128.25 (4.48)	4	126.75 (6.84)	4	0.96 (−3.15, 5.07)	2.04 (−1.48, 5.57)
PMBE	127.30 (5.23)	5	125.10 (6.84)	5	125.00 (6.58)	5	1.57 (−1.88, 5.01)	1.74 (−1.61, 5.09)
Difference[4]							0.61 (−4.76, 5.97)	-0.30 (−5.17, 4.57)
DBP (mmHg)								
Placebo	71.38 (3.45)	4	75.50 (5.08)	4	74.13 (3.82)	4	3.38 (0.006, 6.75)	1.40 (−1.51, 4.31)
PMBE	72.50 (2.77)	5	72.70 (1.93)	5	72.80 (2.68)	5	0.76 (−2.07, 3.58)	0.88 (−1.86, 3.63)
Difference							-2.62 (−7.02, 1.78)	-0.52 (−4.52, 3.49)
Not medicated for high blood pressure								
	Baseline	**n**	**6-weeks**	**n**	**12-weeks**	**n**	**Δ 1 (95 % CI)**	**Δ 2 (95 % CI)**
SBP (mmHg)								
Placebo	135.44 (2.66)	17	135.15 (3.31)	13	132.03 (4.24)	16	-0.71 (−5.36, 3.94)	-3.45 (−7.79, 0.88)
PMBE	136.97 (2.79)	16	131.39 (3.97)	9	129.68 (3.41)	14	-4.05 (−9.40, 1.30)	-7.49 (−12.08, −2.91)**
Difference							-3.34 (−10.43, 3.75)	-4.04 (−10.35, 2.27)
DBP (mmHg)								
Placebo	83.76 (1.91)	17	83.85 (2.54)	13	81.22 (2.28)	16	-1.19 (−3.59, 1.21)	-1.95 (−4.18, 0.29)
PMBE	81.78 (2.64)	16	75.22 (2.82)	9	78.39 (2.65)	14	-2.12 (−4.90, 0.65)	-3.06 (−5.43, −0.70)*
Difference							-0.93 (−4.60, 2.74)	-1.11 (−4.37, 2.14)

[1] Data is presented for individuals with baseline systolic blood pressure > 120 mmHg and who reported whether they were receiving treatment for high blood pressure or not. Data is presented as mean (SEM) or median. Mixed models were used to examine the effect of time within treatment groups as well as the interaction between time and treatment across groups. Data for mixed models is presented as mean estimates (95 % confidence intervals). All data presented is for adjusted models only using pre-specified variables. Significant findings are indicated as $*p < 0.05$, $**p < 0.01$
[2] Effect of time within treatment group from baseline to 6 weeks
[3] Effect of time within treatment group from baseline to 12 weeks (post-intervention)
[4] Interaction between time x treatment is presented as intervention minus control.
DBP, diastolic blood pressure; PMBE, *Pinus massoniana* bark extract; SBP, systolic blood pressure.

with their breakfast. Whether the time of the day when the supplement is taken and whether taken in divided doses or a single dose remains to be established. Grape seed extract is one of the richest sources of PACs and preclinical and clinical studies have demonstrated significant reductions in BP following grape seed extract supplementation.[50,51] Notably, a systematic review and meta-analysis of 16 RCTs reported that grape seed extract significantly lowered SBP (−6.1 mmHg) and DBP (−2.8 mmHg).[50]

Antihypertensive effects of PACs have been thought to be mediated via activation of the nitric oxide system,[52] enhancement of endothelial nitric oxide synthase (eNOS)[53] and inhibition of ACE activity.[54] Significant inhibition of ACE and nicotinamide adenine dinucleotide phosphate oxidase has been shown following PAC intervention and are likely contributing to the antihypertensive biological mechanisms. We have also recently demonstrated a significant reduction in plasma MDA concentrations, a well-established biomarker of lipid peroxidation and oxidative stress (*submitted for publication)*. Since elevated oxidative stress is a key player in the pathogenesis of hypertension,[55,56] this could be an indirect mechanism by which PACs from PMBE modulate BP. This has been reported for the French Maritime pine bark extract, Pycnogenol, which has been shown to possess antihypertensive effects attributed to by protective antioxidant effects against endothelial dysfunction and endothelium-dependent vasorelaxation mediated by eNOS activation.[57] Most of the existing evidence around the antihypertensive mechanisms of PACs has been undertaken utilising PACs derived from grape skin, grape seed extracts and other flavanol-rich compounds like cocoa, therefore, further research is warranted to understand the mechanistic properties of PACs derived from *Pinus massoniana* bark extracts and their product blends.

This study has several strengths such as rigorous study design, being a double-blinded randomized controlled trial; administration of a high-quality dietary supplement already approved by the Australian Therapeutic Goods Administration (AUST L 317661), excellent compliance (>98 % adherence), and although a secondary analyses, power calculations demonstrate > 80 % power to detect a difference in our BP findings by SBP status and BP medication status. Independent biochemical characterization was not conducted on the PMBE which is a limitation of the current study as we are unable to report on lack of adulteration with pharmaceuticals or whether any contamination with heavy metals or other plant materials have occurred. Although we have quantified and reported on key polyphenolic compounds, future studies are warranted to examine the potency of key chemical constituents present in each daily dose of PMBE. Assessment of whether blinding was successful was not conducted in the current study and future studies should assess participants' sensory perception of placebo and PMBE liquids to ensure adequate concealment. Another limitation of the study is that some data for participants at the follow-up timepoints were missing for secondary outcomes, however, this was unavoidable due to the state government public health orders associated with the COVID-19 pandemic at the time. The authors implemented mixed effect regression which addresses missing data in the outcome under the missing at random assumption.

5. Conclusion

This is the first study to report hypotensive effects of a polyphenol-rich dietary supplement derived from PMBE in healthy adults with moderately high SBP. Future clinical studies are warranted to confirm the antihypertensive effects of PMBE in individuals with hypertension. Further research exploring the potential complementary BP modulating effects of PMBE with standard pharmacological therapy may lead to strategies that minimise medication dose-required and/or provide a safe and effective alternative for individuals who are intolerant to BP medications and/or are challenged by poly-pharmacy adherence.

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Author agreement

Our revised manuscript entitled "*Effect of a polyphenol-rich dietary supplement containing Pinus massoniana bark extract on blood pressure in older adults: a parallel, randomized placebo-controlled trial*" is attached for your consideration for publication in Complementary Therapies in Medicine. The data presented in this manuscript is original work has not been previously published elsewhere and is not presently under consideration by any other journal.

All authors have seen and approved the final version of the manuscript being submitted.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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CRediT authorship contribution statement

JJAF and MLG conceptualized and designed the research. JJAF conducted research. JJAF collected and analysed the data. SE assisted with data collection. JJAF and CO devised the statistical plan and methods. CO provided statistical support. JJAF, CO, DB and MLG contributed to writing the paper. JJAF had primary responsibility for drafting the paper and finalising paper for publication. All authors read and approved the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2022.102896.

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