

Communication

Black Garlic and Pomegranate Standardized Extracts for Blood Pressure Improvement: A Non-Randomized Diet-Controlled Study

Federica Fogacci ^{1,2} , Antonio Di Micoli ¹, Elisa Grandi ¹, Giulia Fiorini ¹, Claudio Borghi ^{1,†} 
and Arrigo F. G. Cicero ^{1,2,*} ¹ Hypertension and Cardiovascular Risk Research Group, Medical and Surgical Sciences Department, University of Bologna, 40100 Bologna, Italy² Italian Nutraceutical Society (SINut), 40100 Bologna, Italy

* Correspondence: arrigo.cicero@unibo.it

† These authors contributed equally to this work.

Abstract: Recently released position papers by the European Society of Hypertension (ESH) and the Italian Society of Hypertension (SIIA) provide therapeutic recommendations for the use of nutraceuticals in the management of high blood pressure (BP) and hypertension, opening up new perspectives in the field. This not-randomized diet-controlled clinical study aimed to evaluate if daily dietary supplementation with black garlic and pomegranate (namely SelectSIEVE[®] SlowBeat) could advantageously affect BP in individuals with high-normal BP or stage I hypertension. Enrolled subjects were adhering to a Mediterranean DASH (Dietary Approaches to Stop Hypertension) diet for two weeks before deciding whether to continue following Mediterranean DASH diet alone or in association with SelectSIEVE[®] SlowBeat. At the end of the study, dietary supplementation with SelectSIEVE[®] SlowBeat was associated with significant improvement in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to baseline (Pre-treatment: SBP = 134.3 ± 4.2 and DBP = 88.2 ± 3.4; 4-Week Follow-up: SBP = 130.1 ± 2.8 and DBP = 83.7 ± 2.6). SBP improved also in comparison with control. In conclusion, the study shows that dietary supplementation with extracts from black garlic and pomegranate safely exert significant improvements in BP in healthy individuals adhering to a Mediterranean DASH diet.

Keywords: black garlic; pomegranate; angiotensin-converting enzyme; DASH diet; blood pressure; hypertension



Citation: Fogacci, F.; Di Micoli, A.; Grandi, E.; Fiorini, G.; Borghi, C.; Cicero, A.F.G. Black Garlic and Pomegranate Standardized Extracts for Blood Pressure Improvement: A Non-Randomized Diet-Controlled Study. *Appl. Sci.* **2022**, *12*, 9673. <https://doi.org/10.3390/app12199673>

Academic Editors: Theodoros Varzakas and Maria Antoniadou

Received: 31 August 2022

Accepted: 23 September 2022

Published: 26 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

High blood pressure (BP) and hypertension substantially contribute to the global burden of atherosclerotic cardiovascular disease (ASCVD) [1], and despite affordable and effective antihypertensive treatments being nowadays available, the rates of hypertension treatment and control remain largely perfectible [2]. Current international guidelines emphasize the importance of following the dietary approach to stop hypertension (DASH) and a low-salt Mediterranean diet to improve BP control [3]. DASH and a low-salt Mediterranean diet are not only characterized by sodium restriction (whose effect is largely mediated by ethnicity, age, and presence of specific comorbidities, such as chronic kidney disease or diabetes), but also by a high intake of vegetables (natural sources of nitric oxide and polyphenols), whole grains and low-fat dairy products, and a low intake of red meat, sugar, and trans-hydrogenated fats [4]. Some position papers recently released by the European Society of Hypertension (ESH) and the Italian Society of Hypertension (SIIA) open up new perspectives in the field, providing therapeutic recommendations also for the use of nutraceuticals in the management of high BP and hypertension [5,6]. However, in addition to nutraceuticals that have been traditionally associated with significant improvement in BP control [7], some other foods and natural compounds have recently shown to improve BP levels. Among them are black garlic and pomegranate [8,9].

Allium sativum L. (garlic) anti-hypertensive properties are mainly related to the production of endothelium-active molecules—namely nitric oxide and hydrogen sulfide (H₂S)—leading to vasodilation [10]. Moreover, garlic is a source of gamma-glutamylcysteine that inhibits the activity of angiotensin-converting enzyme (ACE), reduces the formation of ACE-II, and protects the activity of bradykinin [11].

Punica granatum L. (pomegranate) juice is rich in soluble polyphenols comprising anthocyanins and tannins (e.g., ellagitannins—mainly punicalagin—ellagic acid, gallic acid, and catechins) with antioxidant and anti-inflammatory properties, and recognized biological activities, such as ACE inhibition [12,13].

Starting from these assumptions, we aimed to evaluate if daily dietary supplementation with SelectSIEVE® SlowBeat (SelectSIEVE® SlowBeat was manufactured and kindly provided by Roelmi HPC (Milan, Italy)) could advantageously affect BP in individuals with high-normal BP or stage I hypertension as an add-on lifestyle intervention to DASH diet.

2. Methods

2.1. Study Design and Participants

This not-randomized diet-controlled clinical study involved a sample of Italian free-living individuals recruited between April and June 2021 from the Internal Medicine Division's Hypertension Clinic of the S. Orsola Malpighi University Hospital, Bologna, Italy.

Participants were required to be aged 30–70 years, with high-normal BP (systolic blood pressure (SBP)= 130–139 mmHg and/or diastolic blood pressure (DBP)= 85–89 mmHg) or stage I hypertension (SBP= 140–159 mmHg and/or DBP= 90–99 mmHg) [3], and an estimated 10-year CV risk <5% based on SCORE (Systematic CORonary Risk Evaluation) risk charts [14]. Exclusion criteria included diabetes, previous history of ASCVD, obesity (body mass index (BMI) > 30 Kg/m²), uncontrolled thyroid diseases, history of malignancies, use of medication or dietary supplement affecting BP, alcoholism, pregnancy, and breastfeeding.

Enrolled individuals adhered to a Mediterranean Dietary Approaches to Stop Hypertension (DASH) diet for two weeks before allocation and were clinically evaluated at baseline (week 0) and at weeks 2 and 4. The study timeline is described in detail in Figure 1.

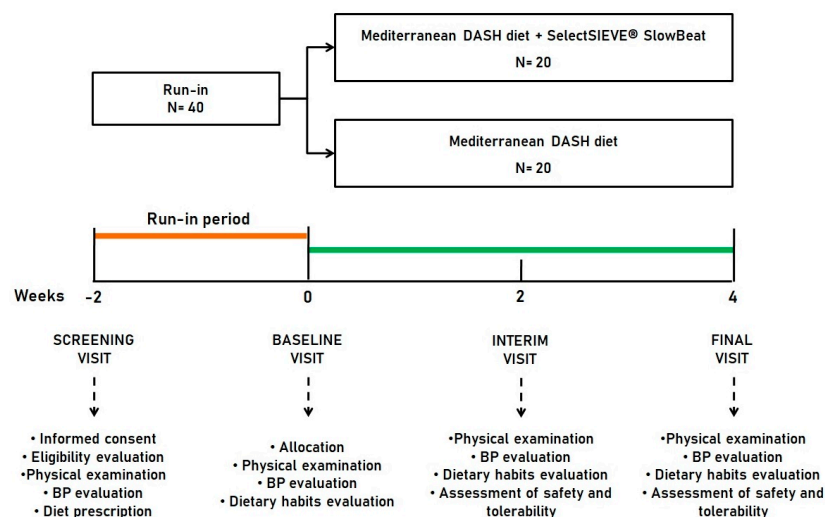


Figure 1. Study timeline. BP = Blood pressure; DASH = Dietary Approaches to Stop Hypertension; N = Number of individuals.

The study fully complied with the ethical principles of the Declaration of Helsinki and later amendments, and with The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and its protocol was approved by the Ethical Committee of the University of Bologna. All patients signed a written informed

consent to participate. The registration of the study on ClinicalTrials.gov is not mandatory because of its non-randomized design.

2.2. Dietary Supplementation

After a 2-week period of standardization, enrolled subjects decided whether to continue following the Mediterranean DASH diet alone or in association with SelectSIEVE[®] SlowBeat, containing black garlic (bulb extract) and pomegranate (fruit extract) as active ingredients, and maltodextrin (from corn) and arabic gum as inactive carriers (Table 1).

Table 1. Quantitative composition of the dietary supplement—namely SelectSIEVE[®] SlowBeat—used in the clinical study.

Active Ingredients	Quantity Per Capsule
Black garlic (<i>Allium Sativum</i> L.)	140 mg
Pomegranate (<i>Punica Granatum</i> L.)	60 mg

Patients allocated to SelectSIEVE[®] SlowBeat were provided with 2 boxes each containing 30 capsules, and were instructed to take 2 capsules of the dietary supplement once daily in the morning, for the entire duration of the study. At the end of the clinical study, all unused capsules were retrieved for inventory and participants' compliance was assessed by counting the number of returned capsules.

The study's product was manufactured and packaged by Roelmi HPC (Milan, Italy) following the Quality Management System ISO 9001:2008 and the European Good Manufacturing Practices (GMP), satisfying requirements in the "Code Of Federal Regulation" title 21, volume 2, part 111.

2.3. Assessments

2.3.1. Clinical Information

Data regarding demographic issues, medical history, allergies, and current medications were collected from volunteers. Validated semi-quantitative questionnaires—including Food Frequency Questionnaire (FFQ)—were used to assess demographic variables, recreational physical activity, and dietary and smoking habits [15].

Height and weight were respectively measured to the nearest 0.1 cm and 0.1 kg, with subjects standing erect with eyes directed straight wearing light clothes and bare feet. Waist circumference (WC) was measured in a horizontal plane at the end of a normal expiration, at the midpoint between the inferior margin of the last rib and the superior iliac crest. Body mass index (BMI) was calculated as body weight in kilograms, divided by height squared in meters (kg/m²).

2.3.2. Blood Pressure Measurements

Resting SBP and DBP were measured with a validated oscillometric device, in accordance with the recommendations of the "European Guidelines for the management of arterial hypertension" [3]. Three BP readings were obtained. The first reading was discarded and the average between the second and the third reading was collected as a study variable. Pulse pressure (PP) was calculated as the difference between SBP and DBP.

2.3.3. Assessment of Safety and Tolerability

Safety and tolerability were evaluated through a continuous monitoring during the study [16]. A 10-point visual analog scale (VAS) was used to measure patients' acceptability of SelectSIEVE[®] SlowBeat.

2.4. Statistical Analysis

Kolmogorov–Smirnov test was used to test the normality distribution of the studied variables. Parameters collected at baseline were compared using Levene's test and Student's

T test, and by the χ^2 test and Fisher's exact test. Between-group differences were evaluated by repeated-measures analysis of variance (ANOVA) and Tukey's post hoc test. All data were reported as means and related standard deviations (SD). A two-tailed p level of <0.05 was considered statistically significant for all tests.

Data were analyzed using intention to treat by means of the Statistical Package for Social Science (SPSS) 26.0, version for Windows.

3. Results

3.1. Analysis of Efficacy

A total of 69 volunteers were assessed for eligibility, and 40 individuals (Men: 23; Women: 17) were enrolled and successfully completed the study according to its design (Figure 2).



CONSORT 2010 Flow Diagram

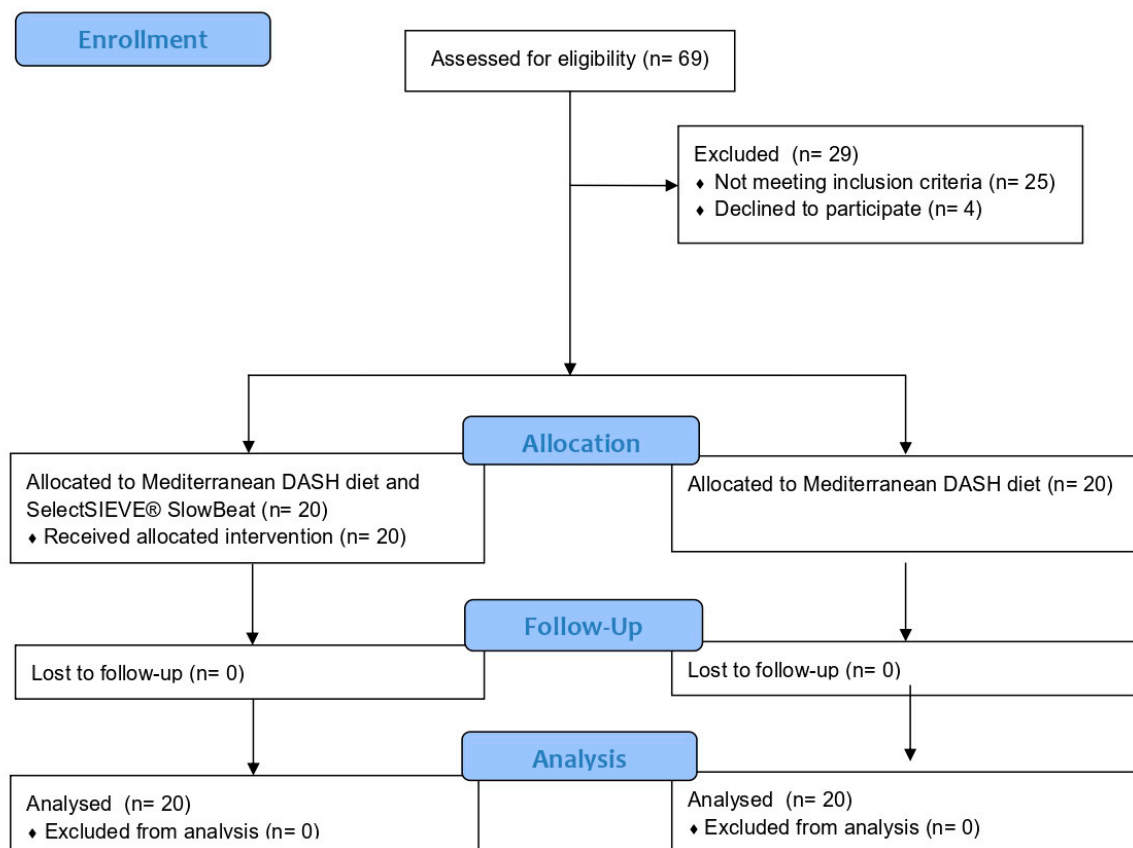


Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

At baseline, the groups were cross-matched in regards to age and the main anthropometric and hemodynamic parameters (Table 2).

Table 2. Anthropometric and hemodynamic parameters from the baseline to the end of the study, reported as means and related standard deviations.

Parameters	Mediterranean DASH Diet + SelectSIEVE® SlowBeat (N. 20)			Mediterranean DASH Diet (N. 20)		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
Age (years)	54.4 ± 3.3			54.9 ± 3.8		
WC (cm)	84.5 ± 6.9	84.2 ± 6.8	84.3 ± 6.6	84.8 ± 6.1	84.4 ± 6.8	84.5 ± 6.7
BMI (kg/m ²)	25.2 ± 1.6	25.1 ± 1.7	25.3 ± 1.8	25.3 ± 1.9	25.2 ± 1.8	25.4 ± 1.6
SBP (mmHg)	134.3 ± 4.2	131.4 ± 3.9	130.1 ± 2.8 * [§]	135.4 ± 3.9	132.9 ± 5.6	133.5 ± 4.3
DBP (mmHg)	88.2 ± 3.4	84.4 ± 4.1	83.7 ± 2.6 *	87.4 ± 4	85.1 ± 4.8	84.4 ± 4.3
PP (mmHg)	46.4 ± 2.2	47.1 ± 1.9	46.4 ± 2.2	48.0 ± 2.9	48.2 ± 3.7	47.3 ± 2.4
HR (bpm)	68.3 ± 4.1	69.4 ± 4.6	67.2 ± 5.6	66.3 ± 4.7	68.1 ± 3.4	65.2 ± 4.9

* $p < 0.05$ versus baseline; [§] $p < 0.05$ versus control. BMI = Body mass index; DASH = Dietary Approaches to Stop Hypertension; DBP = Diastolic blood pressure; HR = Heart rate; PP = Pulse pressure; SBP = Systolic blood pressure; WC = Waist circumference.

At the end of the study, dietary supplementation with SelectSIEVE® SlowBeat resulted in significant improvements in SBP and DBP compared to baseline. SBP improved also in comparison with control (Table 3).

Table 3. Diet composition at enrollment and at the end of the study. Values are expressed as mean ± SD.

Parameters	Baseline	Week 4
Total energy (Kcal/day)	1724 ± 142	1718 ± 157
Carbohydrates(% of total energy)	56.7 ± 3.4	55.9 ± 4.6
Proteins (% of total energy)	18.4 ± 3.2	17.7 ± 3.8
Animal protein (% of total energy)	12.7 ± 1.1	12.4 ± 1.3
Vegetal protein (% of total energy)	5.6 ± 0.6	5.3 ± 1.2
Total fats (% of total energy)	24.9 ± 5.4	26.1 ± 1.8
Saturated fatty acids (% of total energy)	7.1 ± 0.2	7.6 ± 0.1
Monounsaturated fatty acids (% of total energy)	12.9 ± 0.8	13.2 ± 1.4
Polyunsaturated fatty acids (% of total energy)	4.8 ± 0.4	5.3 ± 1.7
Total dietary fibers (g/day)	26.4 ± 2.6	27.7 ± 4.1
Cholesterol (mg/day)	190.9 ± 14.2	189.8 ± 15.4

No statistically significant changes were recorded in dietary habits during the study with any changes in total energy and macronutrient intake (Table 3).

3.2. Analysis of Safety

All participants completed the clinical study according to its design (dropout rate = 0%). No treatment-emergent adverse events were reported during the study. Patients' acceptability of SelectSIEVE® SlowBeat was good and comparable to that of standard care.

4. Discussion

During the last decades, CV epidemiology has focused the attention on normal-high BP and stage I hypertension as an emergent public health issue. In effect, according to the most recent observations, the prevalence of these conditions is about 30% in the general adult population, and they have been clearly associated with an increased risk of developing hypertension (8–20%) [17], hypertension-related target organ damage [18,19], and ASCVD [20], whereas reduced BP associates a decreased risk of CV complications [1].

The most recently released International Guidelines suggest to firstly manage normal-high BP values and stage I hypertension by increasing weekly aerobic physical activity and reducing the overall energy intake with the ultimate aim to maintain the BMI between 20 and 25 kg/m² (or keeping the waist size to less than 94 cm for men and 80 cm for women) [5]. Other recommendations from ESH include the urgency to reduce the daily intake of alcohol, salt (<5 gr/day), and processed meat, by increasing the intake of vegetables, olive oil, and low-fat dairy products, and refraining from passive and active cigarette smoking [5].

Even though the aforementioned lifestyle measures are undoubtedly effective, they are not always sufficient to manage BP levels, even in low-risk individuals. For this reason, during the last years, pre-clinical and clinical investigators have been searching for natural compounds with a detectable BP lowering effect in humans [21]. Therefore, a constantly growing body of evidence supports the use of a number of nutraceuticals in reducing BP, with some specificities relating to different mechanisms of action and pleiotropic effects [21].

Previous studies on black garlic indicated a food with higher levels of reducing sugars, organic acids, and bioactive compounds (particularly S-allyl-cysteine and coumaric acid) than fresh garlic [22]. In effect, the consumption of aged black garlic has been recently associated to clinically detectable improvements in a number of CV risk factors, as long as the extent of these effects has been shown to be dependent on the garlic aging process and the amount and type of accumulated chemical compounds [23]. Recently, a randomized double blind crossover clinical study involving a sample of 67 hypercholesterolemic individuals showed that the consumption of 250 mg aged black garlic extract with 1.25 mg S-allyl-L-cysteine was able to significantly decrease DBP after 6 weeks of daily dietary supplementation [8]. As suggested by the authors, the mechanisms of action by which aged black garlic could modulate BP involve antioxidant activity by organosulfur compounds, the regulation of transcription factors involved in hypertension, and ACE regulation [24]. In this context, animal studies had already shown that black garlic extracts and their bioactive compounds have a greater inhibitory effect on endothelial ACE activity than normal garlic extracts (88.8% versus 52.7%) [25].

In the latest years, pomegranate has also gained widespread popularity as a functional food and nutraceutical source, and its consumption has been studied in relation to a variety of chronic diseases including CV diseases [26]. A systematic review and meta-analysis of randomized clinical studies suggested consistent benefits of pomegranate juice consumption on both SBP and DBP, with an effect on SBP that was independent from the duration of dietary supplementation [9]. Moreover, pomegranate juice was shown to significantly reduce intensity, occurrence, and duration of angina pectoris in patients with unstable angina [27].

In our study, combined dietary supplementation with aged black garlic and pomegranate extracts was associated with significant improvements in SBP and DBP. These findings are particularly interesting, since the treatment-related decreases in BP levels were experienced by individuals who were already following a Mediterranean DASH diet, that represents the gold-standard treatment for patients with high-normal BP and the first-stage treatment for patients with stage I hypertension and low-to-intermediate ASCVD risk, as collegially recommended by the European Society of Cardiology (ESC) and ESH [3]. Moreover, the BP-lowering effect that dietary supplementation with aged black garlic and pomegranate extracts can bring about is clinically relevant in addition to being statistically significant, since previous evidence showed that prolonged reduction in SBP also by 2 mmHg result in a 7% reduced incidence of death secondary to stroke and in a 10% reduced incidence of death secondary to other vascular etiology [28].

Certainly, some limitations need to be acknowledged, such as the small sample size, the short follow-up and—definitely—the pilot and non-randomized nature of the study design. Moreover, the lack of a placebo group did not allow judgement of nocebo and placebo effects. On the other side, the enrolled individuals maintained a similar dietary pattern during the study, so that we have no reason to think that the observed hemodynamic effects were due to changes in food consumption and nutrient intake rather than SelectSIEVE®

SlowBeat. Additionally, this study design simulates the clinical practice setting, where these kinds of patients are usually managed in a less intensive way than in a standard randomized clinical trial. However, more research is needed that focuses on the underlying reasons and mechanisms of the effects observed during the study. Furthermore, it remains to be assessed whether combined dietary supplementation with aged black garlic and pomegranate extracts could also improve vascular aging, by reducing arterial stiffness and increasing endothelial reactivity.

The relevance of our findings lies in the fact that an increased consumption of food bioactive compounds configures as a well-tolerated and effective strategy to improve BP control. Moreover, this result has to be interpreted in light of previous evidence showing that effective BP control can only be achieved through a comprehensive strategy of prevention at the individual and population levels, with the use of non-pharmacological interventions throughout the life course [29].

5. Conclusions

Finally, the study shows that dietary supplementation with extracts from black garlic and pomegranate safely exert significant improvements in BP in healthy individuals adhering to a Mediterranean DASH diet.

Author Contributions: Conceptualization, A.F.G.C.; methodology, A.F.G.C. and F.F.; software, A.F.G.C.; formal analysis, A.F.G.C.; investigation, A.F.G.C., F.F., A.D.M., E.G. and G.F.; data curation, F.F., A.D.M., E.G. and G.F.; writing—original draft preparation, A.F.G.C. and F.F.; writing—review and editing, A.D.M., E.G., G.F. and C.B.; supervision, C.B.; project administration, A.F.G.C.; funding acquisition, A.F.G.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study (BP_open2021) was approved by the Local Institutional Review Board (Code: LLD-RP2018) and was conducted following the Declaration of Helsinki and later amendments.

Informed Consent Statement: Informed consent was obtained from all volunteers involved in the study.

Data Availability Statement: Data supporting the study's findings are available upon request from the corresponding author with the permission of the University of Bologna.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Del Pinto, R.; Grassi, G.; Muiesan, M.L.; Borghi, C.; Carugo, S.; Cicero, A.F.G.; Di Meo, L.; Iaccarino, G.; Minuz, P.; Mulatero, P.; et al. World Hypertension Day 2021 in Italy: Results of a Nationwide Survey. *High Blood Press. Cardiovasc. Prev.* **2022**, *29*, 353–359. [[CrossRef](#)]
2. Borghi, C.; Fogacci, F.; Agnoletti, D.; Cicero, A.F.G. Hypertension and Dyslipidemia Combined Therapeutic Approaches. *High Blood Press. Cardiovasc. Prev.* **2022**, *29*, 221–230. [[CrossRef](#)] [[PubMed](#)]
3. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.; Coca, A.; De Simone, G.; Dominiczak, A.; et al. List of authors/Task Force members: 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J. Hypertens.* **2018**, *36*, 2284–2309. [[CrossRef](#)] [[PubMed](#)]
4. Cicero, A.F.G.; Veronesi, M.; Fogacci, F. Dietary Intervention to Improve Blood Pressure Control: Beyond Salt Restriction. *High Blood Press. Cardiovasc. Prev.* **2021**, *28*, 547–553. [[CrossRef](#)] [[PubMed](#)]
5. Borghi, C.; Tsioufis, K.; Agabiti Rosei, E.; Burnier, M.; Cicero, A.F.G.; Clement, D.; Coca, A.; Desideri, G.; Grassi, G.; Lovic, D.; et al. Nutraceuticals and blood pressure control: A European Society of Hypertension position document. *J. Hypertens.* **2020**, *38*, 799–812. [[CrossRef](#)]
6. Cicero, A.F.G.; Grassi, D.; Tocci, G.; Galletti, F.; Borghi, C.; Ferri, C. Nutrients and Nutraceuticals for the Management of High Normal Blood Pressure: An Evidence-Based Consensus Document. *High Blood Press. Cardiovasc. Prev.* **2019**, *26*, 9–25. [[CrossRef](#)]
7. Cicero, A.F.G.; Fogacci, F.; Colletti, A. Food and plant bioactives for reducing cardiometabolic disease risk: An evidence based approach. *Food Funct.* **2017**, *8*, 2076–2088. [[CrossRef](#)]

8. Valls, R.M.; Companys, J.; Calderón-Pérez, L.; Salamanca, P.; Pla-Pagà, L.; Sandoval-Ramírez, B.A.; Bueno, A.; Puzo, J.; Crescenti, A.; Bas, J.M.D.; et al. Effects of an Optimized Aged Garlic Extract on Cardiovascular Disease Risk Factors in Moderate Hypercholesterolemic Subjects: A Randomized, Crossover, Double-Blind, Sustained and Controlled Study. *Nutrients* **2022**, *14*, 405. [[CrossRef](#)]
9. Sahebkar, A.; Ferri, C.; Giorgini, P.; Bo, S.; Nachtigal, P.; Grassi, D. Effects of pomegranate juice on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* **2017**, *115*, 149–161. [[CrossRef](#)]
10. Zadhoush, R.; Alavi-Naeini, A.; Feizi, A.; Naghshineh, E.; Ghazvini, M.R. The effect of garlic (*Allium sativum*) supplementation on the lipid parameters and blood pressure levels in women with polycystic ovary syndrome: A randomized controlled trial. *Phytother. Res.* **2021**, *35*, 6335–6342. [[CrossRef](#)]
11. Gao, X.; Xue, Z.; Ma, Q.; Guo, Q.; Xing, L.; Santhanam, R.K.; Zhang, M.; Chen, H. Antioxidant and antihypertensive effects of garlic protein and its hydrolysates and the related mechanism. *J. Food Biochem.* **2020**, *44*, e13126. [[CrossRef](#)] [[PubMed](#)]
12. Sohrab, G.; Roshan, H.; Ebrahimof, S.; Nikpayam, O.; Sotoudeh, G.; Siasi, F. Effects of pomegranate juice consumption on blood pressure and lipid profile in patients with type 2 diabetes: A single-blind randomized clinical trial. *Clin. Nutr. ESPEN* **2019**, *29*, 30–35. [[CrossRef](#)] [[PubMed](#)]
13. Stowe, C.B. The effects of pomegranate juice consumption on blood pressure and cardiovascular health. *Complement. Ther. Clin. Pract.* **2011**, *17*, 113–115. [[CrossRef](#)] [[PubMed](#)]
14. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* **2019**, *290*, 140–205. [[CrossRef](#)]
15. Fogacci, F.; Rizzoli, E.; Giovannini, M.; Bove, M.; D’Addato, S.; Borghi, C.; Cicero, A.F.G. Effect of Dietary Supplementation with Eufortyn[®] Colesterolo Plus on Serum Lipids, Endothelial Reactivity, Indexes of Non-Alcoholic Fatty Liver Disease and Systemic Inflammation in Healthy Subjects with Polygenic Hypercholesterolemia: The ANEMONE Study. *Nutrients* **2022**, *14*, 2099. [[CrossRef](#)]
16. Cicero, A.F.G.; Fogacci, F.; Veronesi, M.; Strocchi, E.; Grandi, E.; Rizzoli, E.; Poli, A.; Marangoni, F.; Borghi, C. A randomized Placebo-Controlled Clinical Trial to Evaluate the Medium-Term Effects of Oat Fibers on Human Health: The Beta-Glucan Effects on Lipid Profile, Glycemia and inTestinal Health (BELT) Study. *Nutrients* **2020**, *12*, 686. [[CrossRef](#)]
17. Vasan, R.S.; Larson, M.G.; Leip, E.P.; Evans, J.C.; O’Donnell, C.J.; Kannel, W.B.; Levy, D. Impact of high-normal blood pressure and the risk of cardiovascular disease. *N. Engl. J. Med.* **2001**, *345*, 1291–1297. [[CrossRef](#)]
18. Cuspidi, C.; Sala, C.; Tadic, M.; Gherbesi, E.; Fachetti, R.; Grassi, G.; Mancia, G. High-normal blood pressure and abnormal left ventricular geometric patterns: A meta-analysis. *J. Hypertens.* **2019**, *37*, 1312–1319. [[CrossRef](#)]
19. Cuspidi, C.; Sala, C.; Tadic, M.; Gherbesi, E.; Grassi, G.; Mancia, G. Pre-hypertension and subclinical carotid damage: A meta-analysis. *J. Hum. Hypertens.* **2019**, *33*, 34–40. [[CrossRef](#)]
20. Egan, B.M.; Stevens-Fabry, S. Prehypertension-prevalence, health risks, and management strategies. *Nat. Rev. Cardiol.* **2015**, *12*, 289–300. [[CrossRef](#)]
21. Strilchuk, L.; Cincione, R.I.; Fogacci, F.; Cicero, A.F.G. Dietary interventions in blood pressure lowering: Current evidence in 2020. *Kardiol. Pol.* **2020**, *78*, 659–666. [[CrossRef](#)] [[PubMed](#)]
22. Imaizumi, V.M.; Laurindo, L.F.; Manzan, B.; Guiguer, E.L.; Oshiiwa, M.; Otoboni, A.M.M.B.; Araujo, A.C.; Tofano, R.J.; Barbalho, S.M. Garlic: A systematic review of the effects on cardiovascular diseases. *Crit. Rev. Food Sci. Nutr.* **2022**, *Online ahead of print*. [[CrossRef](#)] [[PubMed](#)]
23. Kimura, S.; Tung, Y.C.; Pan, M.H.; Su, N.W.; Lai, Y.J.; Cheng, K.C. Black garlic: A critical review of its production, bioactivity, and application. *J. Food Drug Anal.* **2017**, *25*, 62–70. [[CrossRef](#)] [[PubMed](#)]
24. Ried, K.; Fakler, P. Potential of garlic (*Allium sativum*) in lowering high blood pressure: Mechanisms of action and clinical relevance. *Integr. Blood Press. Control* **2014**, *7*, 71–82. [[CrossRef](#)]
25. Ahmed, T.; Wang, C.K. Black Garlic and Its Bioactive Compounds on Human Health Diseases: A Review. *Molecules* **2021**, *26*, 5028. [[CrossRef](#)]
26. Laurindo, L.F.; Barbalho, S.M.; Marquess, A.R.; Grecco, A.I.S.; Goulart, R.A.; Tofano, R.J.; Bishayee, A. Pomegranate (*Punica granatum* L.) and Metabolic Syndrome Risk Factors and Outcomes: A Systematic Review of Clinical Studies. *Nutrients* **2022**, *14*, 1665. [[CrossRef](#)]
27. Razani, Z.; Dastani, M.; Kazerani, H.R. Cardioprotective Effects of Pomegranate (*Punica granatum*) Juice in Patients with Ischemic Heart Disease. *Phytother. Res.* **2017**, *31*, 1731–1738. [[CrossRef](#)]
28. Lewington, S.; Clarke, R.; Qizilbash, N.; Peto, R.; Collins, R.; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **2002**, *360*, 1903–1913. [[CrossRef](#)]
29. Zhou, B.; Perel, P.; Mensah, G.A.; Ezzati, M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat. Rev. Cardiol.* **2021**, *18*, 785–802. [[CrossRef](#)]