Received: 10 August 2022 | Revised: 9 May 2023 | Accepted: 30 June 2023

DOI: 10.1002/ptr.7951

RESEARCH ARTICLE

WILEY

Effect of dietary supplementation with Diuripres® on blood pressure, vascular health, and metabolic parameters in individuals with high-normal blood pressure or stage I hypertension: The CONDOR randomized clinical study

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Funding information
Neopharmed Gentili S.p.A.

Abstract

Our aim was to evaluate if a nutritional intervention with a dietary supplement (Diuripres®) containing magnesium, standardized extract of orthosiphon, hawthorn, and hibiscus could positively affect blood pressure (BP), vascular health, and metabolic parameters in 60 individuals with high-normal BP or stage I hypertension. Participants followed a low-fat low-sodium Mediterranean diet for 4 weeks before being randomly allocated to 8-week treatment with two pills each day of either Diuripres® or placebo. Diuripres® significantly decreased systolic BP compared to placebo after 4 weeks (3.1 ± 0.8 mmHg; $p < 0.05$) and more consistently after 8 weeks (3.4 ± 0.9 mmHg; $p < 0.05$). At 8-week follow-up, after correction for multiple testing, dietary supplementation with Diuripres® was associated with significant improvements in diastolic BP (−3.1 ± 0.6 mmHg; $p < 0.05$), aortic BP (−4.3 ± 0.4 mmHg; $p < 0.05$), and high-sensitivity C-reactive protein (hs-CRP; 0.04 ± 0.01 mg/dL; $p < 0.05$) in comparison with baseline. The reductions in diastolic BP (−-3.8 ± 0.7 mmHg; $p < 0.05$), aortic BP (−5.2 ± 1.0 mmHg; $p < 0.05$), and hs-CRP (−0.03 ± 0.01 mg/dL; $p < 0.05$) were also significant compared to placebo. Therefore, our study shows that dietary supplementation with Diuripres® may be useful in individuals with high-normal BP or stage I hypertension.

KEYWORDS
blood pressure, dietary supplement, hawthorn, hibiscus, hypertension, magnesium, nutraceutical, orthosiphon

1 | INTRODUCTION

High blood pressure (BP) and hypertension substantially contribute to the global burden of atherosclerotic cardiovascular disease (CVD; Del Pinto et al., 2022). Several reports have recently shown that hypertensive individuals often have additional cardiovascular (CV) and metabolic risk factors (e.g., hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, and diabetes), which further contribute to

increase the individual risk of developing hypertension-related complications (Volpe et al., 2012). Lifestyle and dietary changes can be adopted as effective therapies to lower BP and other CV risk factors. However, adherence to lifestyle recommendations is often poor (Strilchuk et al., 2020). Moreover, despite affordable and effective antihypertensive treatments being nowadays available, the rates of hypertension treatment and control remain largely perfectible, and optimization of CV risk management remains a challenge (Borghi et al., 2022). In this context, the European Society of Hypertension (ESH) and the Italian Society of Hypertension (SIIA) summarized evidence from literature and provided therapeutic recommendations for the use of nutraceutical compounds in the management of high BP and hypertension (Borghi et al., 2020; Cicero et al., 2019). In effect, this approach may be effective for the management of CV risk at the population level, and could integrate the benefit of drug treatment contributing to a "tailored" approach to risk factors proportional to the individual risk profile (Borghi et al., 2020; Cicero et al., 2019).

Accumulating evidence suggests that magnesium oxide may affect BP regulation through the direct stimulation of prostacyclin and nitric oxide formation, the modulation of endothelium-dependent, and endothelium-independent vasodilation, by reducing vascular tone and reactivity and preventing vascular injury through anti-inflammatory and antioxidant effects (Rosanoff et al., 2021). Moreover, increasing the dietary intake of anthocyanins—which are naturally present in fruit and vegetables—has been historically associated with a decreased risk of all-cause mortality (Aune et al., 2017), with recent evidence demonstrating their effectiveness in reducing high BP, hypertension, and plasma lipids concentrations (Fairlie-Jones et al., 2017). Starting from these previous observations, we aimed to evaluate if chronic treatment with a dietary supplement (Diuripres®) containing magnesium oxide, standardized dry extracts of orthosiphon (*Orthosiphon stamineus Benth*), hawthorn (*Crataegus curvisepala Lind.*), and hibiscus (*Hibiscus sabdariffa L.*) could positively affect BP (primary outcome), and vascular health and metabolic parameters (secondary outcomes) in individuals with high-normal BP or stage I hypertension.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was designed as a randomized, double-blind, parallel-group, placebo-controlled clinical study, and involved a sample of Italian volunteers with high-normal BP or stage I hypertension recruited from the Hypertension Clinic of the S. Orsola Malpighi University Hospital (Bologna, Italy).

Study's participants were required to be aged between 18 and 70 years, with high-normal BP (SBP = 130–139 mmHg and/or DBP = 85–89 mmHg) or stage I hypertension (SBP = 140–159 mmHg and/or DBP = 90–99 mmHg; Williams et al., 2018), and an estimated 10-year CV risk <5% according to the SCORE (Systematic COronary Risk Evaluation) risk charts (Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies, 2019). Exclusion criteria included previous history of CVD, type 1 or type 2 diabetes, obesity (body mass index (BMI) > 30 kg/m^2), a positive test for human immunodeficiency virus (HIV) or viral hepatitis (HBV, HCV, or HEV), uncontrolled thyroid diseases, history of malignancies, stable lipid-lowering treatment for at least 4 weeks, use of medication or nutritional supplement that altered blood pressure levels, use of anticoagulants, alcoholism, pregnancy, and breastfeeding.

Enrolled subjects were adhering to a low-sodium low-fat Mediterranean diet for 4 weeks before randomization. This phase was needed to eventually exclude subjects not able to comply with an overall healthy diet and to educate patients to avoid dietary behaviors potentially affecting blood pressure levels during the study. The intervention period lasted 8 weeks. Before, in the middle and after the treatment, the patients were evaluated for clinical status, and by the execution of a physical examination and laboratory and hemodynamic analyses. The timeline of the study is reported in detail in Figure 1.

The study fully complied with the Ethical Principles for Medical Research Involving Human Subjects of the Declaration of Helsinki and

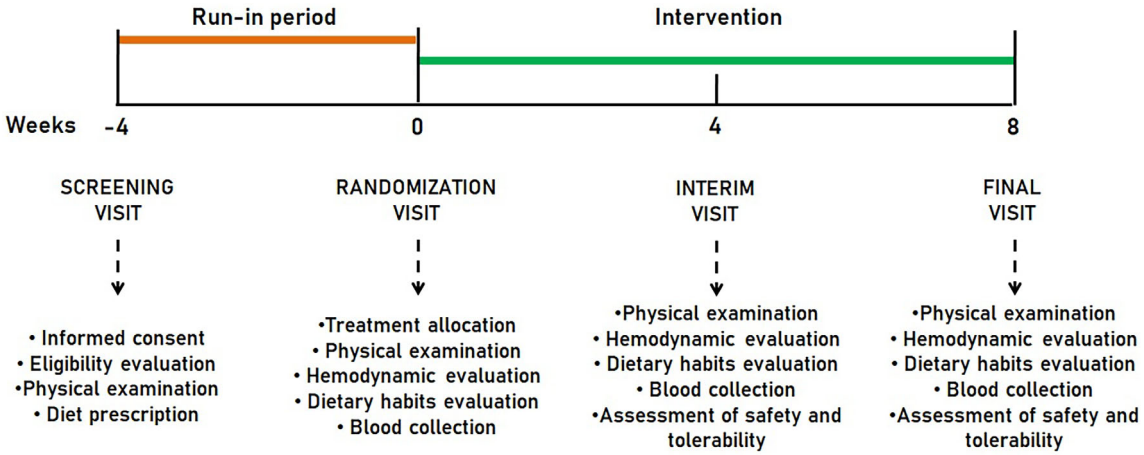

FIGURE 1 Timeline of the study.

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). The study protocol was approved by the Ethical Committee of the University of Bologna and registered in ClinicalTrials.gov (ID: NCT05167747). All patients signed a written informed consent to participate.

2.2 | Treatment

After 4-week period of diet standardization, enrolled subjects were randomized to receive either two indistinguishable pills daily of placebo or Diuripres®, containing magnesium oxide, standardized dry extracts of orthosiphon (*Orthosiphon stamineus Benth*), hawthorn (*Crataegus curvisepala Lind.*), and hibiscus (*Hibiscus sabdariffa L.*) as active ingredients (Table 1). Quality specifications of Diuripres® were included in the Supporting Information.

The study products were manufactured and packaged by the Production facilities of Neopharmed Gentili S.p.A., which followed the Quality Management System ISO 9001:2008 and the European Good Manufacturing Practices (GMP), satisfying requirements in "Code Of Federal Regulation" title 21, volume 2, part 111.

At the time of randomization, each patient was provided with boxes containing 120 tablets (either active ingredients or placebo).

Randomization was centrally performed by computer-generated codes. Participants and investigators were blinded to the group assignment. Randomization codes were kept in a sealed envelope that was opened after study completion and data analysis.

For the entire duration of the study, patients were instructed to take two pills of the assigned treatment once daily, early in the morning.

At the end of the clinical trial, all unused pills were retrieved for inventory. Participants' compliance was assessed by counting the number of returned pills. A mean compliance was calculated by the percentage ration of the number of returned pills to the number of pills expected to have been consumed based on the number of days of active treatment during the study. A single patient was defined as compliant when she/he consumed more than 90% of pills he should have consumed during the trial.

TABLE 1 Qualitative and quantitative composition of Diuripres®.

Ingredients	Quantity per tablet (mg)
Orthosiphon d.e. (*Orthosiphon stamineus Benth*)	250
Hawthorn d.e. (*Crataegus curvisepala* Lind.)	160
Hibiscus flower d.e. (*Hibiscus sabdariffa L.*)	80
Magnesium oxide	19
Cellulose E 460	212.75
Calcium phosphates E 341	95
Cross-linked sodium carboxymethyl cellulose E468	28.5
Magnesium stearate E 470b	19
Silicon dioxide E 551	4.75
Nutraficient® white powder	28.22

Abbreviation: d.e., dry extract.

2.3 | Assessments

2.3.1 | Clinical data and anthropometric measurements

Information gathered in the patients' history included the presence of atherosclerotic CVD (ASCVD) and other systemic diseases, allergies, and medications. Validated semi-quantitative questionnaires were used to assess demographic variables, recreational physical activity, and smoking habits (Cicero, Caliceti, et al., 2017). Dietary habits were assessed by the use of a Food Frequency Questionnaire (FFQ; Cicero, Caliceti, et al., 2017).

Quantification and analysis of energy intake and daily diet composition were performed with the MètaDieta® software (INRAN/IEO 2008 revision/ADI), and data were handled in compliance with the company procedure IOA87.

Waist and hip circumferences were measured to the nearest 0.1 cm using a flexible narrow nonstretch tape, in a horizontal plane and at the end of a normal expiration. Waist circumference (WC) was assessed at the midpoint between the inferior margin of the last rib and the superior iliac crest; while hip circumference was measured at the largest circumference around the buttocks.

Height and weight were measured respectively to the nearest 0.1 cm and 0.1 kg, with subjects standing erect with eyes directed straight wearing light clothes and bare feet. The index of central obesity (ICO) resulted from WC to height ratio (Parikh, 2011). Finally, BMI was calculated as body weight in kilograms, divided by height squared in meters (kg/m^2).

2.3.2 | Bioelectrical impedance analysis

Fat mass, lean mass, and total body water (TBW) were estimated through a tetrapolar impedance analyzer (BIA 450 Bioimpedance Analyser; ESCO S.r.l., Rho, Italy). During the measurement, the patients were laying on a non-conducting table in a supine position, without shoes and socks, with the limbs distanced from the body and the legs apart. The receiving electrodes were attached at the dorsal surfaces of the right hand and foot, while the sensing electrodes were placed at the distal end of the metacarpal and metatarsal–phalangeal joints. A current of 800 mA was applied. A frequency of 50 kHz was transmitted at the distal electrodes of the hand and foot.

2.3.3 | Laboratory analyses

Biochemical analyses were carried out on venous blood withdrawn after overnight fasting (at least 12 h). Serum was obtained by the

addition of disodium ethylenediaminetetraacetate (Na_2EDTA; 1 mg/mL) and blood centrifugation at 3000 RPM for 15 min at 25°C.

Trained personnel performed laboratory analyses immediately after centrifugation, according to standardized methods (Cicero, Fogacci, et al., 2021). The following parameters were directly assessed: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine, serum uric acid (SUA), high-sensitivity C-reactive protein (hs-CRP), gamma-glutamyl transferase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST).

LDL-C was obtained by the Friedewald formula. Non-HDL cholesterol (Non-HDL-C) resulted from the difference between TC and HDL-C. The glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-epi) equation (Levey et al., 2009).

Lipid accumulation product (LAP) was calculated as (WC − 65) × TG (expressed in mmol/L) for men and (WC − 58) × TG (expressed in mmol/L) for women (Bedogni et al., 2010). Fatty liver index (FLI) was calculated as follows: $[e^{0.953 \times \ln (TG) + 0.139 \times BMI + 0.718 \times \ln (GGT) + 0.053 \times WC - 15.745}/(1 + e^{0.953 \times \ln (TG) + 0.139 \times BMI + 0.718 \times \ln (GGT) + 0.053 \times WC - 15.745})] \times 100$ (Cicero et al., 2018). Finally, visceral adiposity index (VAI) was the resulting product from {WC/[39.68 + (1.88 × BMI)]} × (TG (expressed in mmol/L)/1.03) × (1.31/HDL-C (expressed in mmol/L)) for men, and from {WC/[36.58 + (1.89 × BMI)]} × (TG (expressed in mmol/L)/0.81) × (1.52/HDL-C (expressed in mmol/L)) for women (Amato et al., 2010).

2.3.4 | Blood pressure measurements

Blood pressure (BP) was measured in accordance with the recommendations of the International Guidelines for the management of arterial hypertension (Williams et al., 2018). Resting systolic (SBP) and diastolic BP (DBP) were measured with a validated oscillometric device and a cuff of the appropriate size was applied on the right upper arm. To improve detection accuracy, three BP readings were sequentially obtained at 1-min intervals. The first reading was discarded, and the average between the second and the third reading was recorded as study variable. Pulse pressure (PP) resulted from the difference between SBP and DBP.

2.3.5 | Pulse wave analysis

Pulse wave analysis (PWA) was noninvasively assessed through a validated cuff-based oscillometric device (Vicorder®, Skidmore Medical Ltd, Bristol, UK) deriving central BP curves using a brachial-to-aortic transfer function. PWA was recorded in each patient supine and at rest, with a cuff applied at the right upper arm. Augmentation Index (AIx) was calculated as the ratio of the pressure increment caused by the reflected wave (augmented pressure) to the pulse pressure (Ageenkova & Purygina, 2011). As previously shown, it represents a measure of the arterial stiffness and is a marker of cardiovascular risk (van Bortel et al., 2012). The intensity of the wave reflection depends on the diameter and the elasticity of the small arteries and arterioles (Stoner et al., 2012) and is inversely related to the body height (Smulyan et al., 1998) and heart rate (Gatzka et al., 2001; Wilkinson et al., 2000). Vicorder® guarantees an excellent intra- and inter-operator reliability (McGreevy et al., 2013).

2.3.6 | Endothelial reactivity

Endothelial function of the arterial vasculature is an important early marker of atherosclerosis, reflecting the ability of the endothelial layer to release nitric oxide (NO), modulating smooth muscle tone in the arterial wall of the conduit arteries (Thijssen et al., 2019).

Following the current guidelines (Corretti et al., 2002), endothelial function was evaluated through Endocheck® (BC Biomedical Laboratories Ltd, Vancouver, BC, Canada), embedded within the Vicorder® device. The measurement was carried out with patients in supine position and in abstinence from cigarette smoking and caffeinated beverages for at least 12 h. After a 10-min rest, the brachial pulse volume (PV) waveforms were recorded at baseline for 10 s and during reactive hyperemia. The BP cuff was inflated to 200 mmHg for 5 min and PV waveforms were recorded for 3 min after cuff released. Endothelial reactivity (ER) was calculated as change in the PV waveform area, comparing waveforms before and during hyperemia through the equation $\sqrt{PV2/PV1}$, where PV1 represents PV at the baseline and PV2 represents PV during hyperemia (Day et al., 2013).

2.3.7 | Assessment of safety and tolerability

Safety and tolerability were evaluated through a continuous monitoring during the study, in order to detect any adverse events, clinical safety, laboratory findings, vital sign measurements, and physical examinations. A blinded, independent expert clinical event committee was appointed by the principal investigator in order to categorize the adverse events that could possibly be experienced during the trial as not related, unlikely related, possibly related, probably related, or definitely related to the tested treatment (Cicero et al., 2020).

2.4 | Statistical analysis

Data were analyzed using intention to treat by means of the Statistical Package for Social Science (SPSS) 25.0, version for Windows.

Based on previously published research, the sample size needed to detect a 3 mmHg between-group mean difference in DBP was of 21 subjects per group, assuming a power of 0.90 and an alpha error of 0.05. This sample size was also enough to detect a 2 mmHg between-group mean difference in SBP. Considering the risk of non-compliance to diet and/or treatment, and of withdrawal from the study, we enrolled 30 patients per group.

As per protocol, we decided a priori to check the efficacy of treatments in subjects assuming at least 90% of the tested products doses foreseen by the trial design.

Kolmogorov–Smirnov test was used to test the normality distribution of the studied variables. When variable were non-normally distributed, they were log-transformed before further statistical testing. Baseline characteristics of the population were compared using independent Student's *t*-test and χ^2 test followed by Fisher's exact test. Then, we carried out an analysis of variance (ANOVA) for repeated measures with two study factors: the within-subject factor (time: baseline, 4 weeks, and 8 weeks) and between-subject factor (intervention: Diuripres® and placebo) for paired data. Benjamini–Hochberg correction, fixing the false discovery rate (FDR) at $\alpha < 0.05$, was used to account for multiple comparisons (Benjamin & Yekutieli, 2001; Cicero et al., 2020). All tests were two-sided. A *p*-level of <0.05 was considered significant for all tests.

3 | RESULTS

3.1 | Efficacy analysis

A total of 147 volunteers was consecutively assessed for eligibility. Sixty patients entered the run-in period and underwent randomization from October 2021 through January 2022. All enrolled subjects successfully completed the trial according to the study design (Figure 2).

All enrolled subjects were considered compliant (i.e., ≥90% of pills assumed) to the treatment. Mean compliance to the treatment was 96% in the active treated group and 98% in the placebo group.

Age range was similar between groups: 41–68 years old in the Diuripres® treated subjects and 43–69 in the placebo-treated ones. The final distribution by sex did not show any significant differences between groups ($p > 0.05$), with 18 women allocated to placebo and 17 women allocated to Diuripres® and no detectable interaction effect.

During the run-in period, no statistically significant changes in the anthropometric parameters were recorded ($p > 0.05$), even if a non-statistically significant trend toward body weight decrease was observed in both treatment groups. Individuals randomized to Diuripres® showed no change in SBP and DBP. Similarly, individuals randomized to placebo experienced no changes in SBP and DBP (Table 2). No statistically significant changes were recorded in the dietary habits of the enrolled individuals from randomization until the end of the study, without any changes in total energy and macronutrient intake (Table 3). Physical activity intensity distribution was similar in both groups and maintained during the study, as well.

Study groups were well matched for all the considered variables at baseline (Table 4).

Diuripres® significantly decreased SBP compared to baseline after 4 weeks and more consistently after 8 weeks (Table 4). At 8-week follow-up, dietary supplementation with Diuripres® was associated with

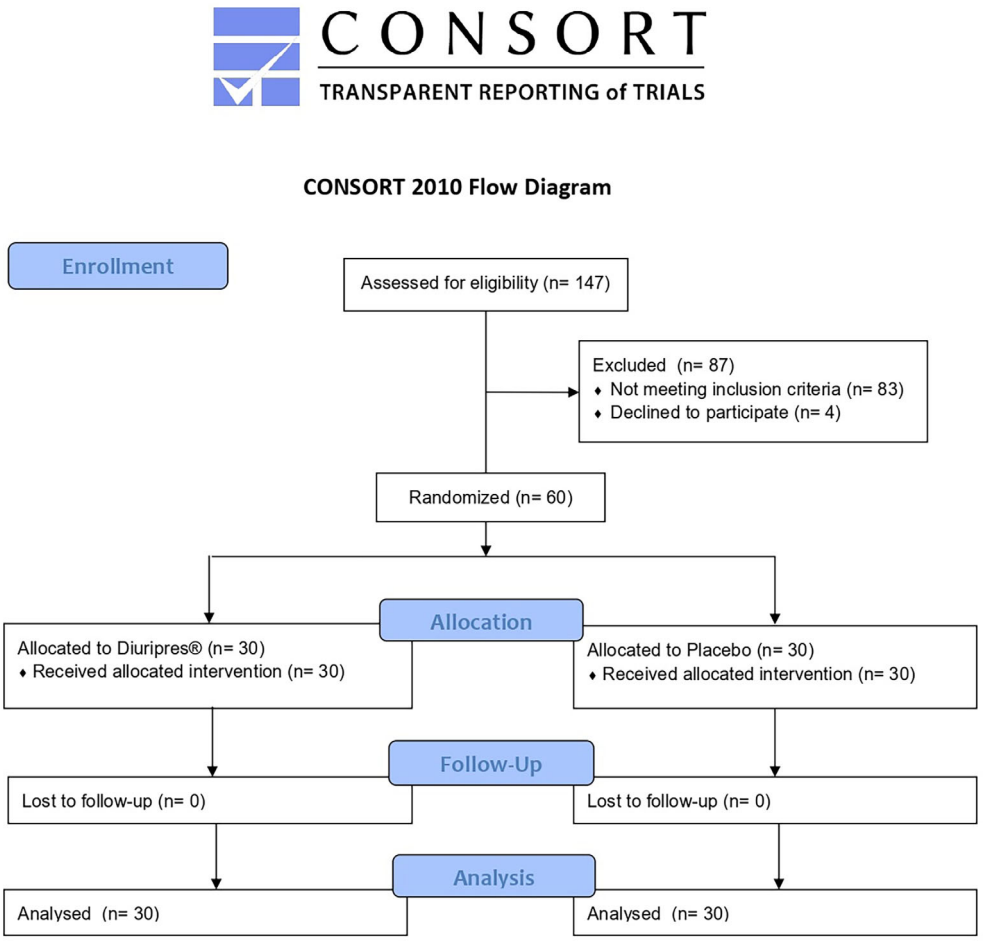

FIGURE 2 CONSORT flow diagram of the progress through the phases of the clinical study.

TABLE 2 Pre-run-in and post-run-in values, reported as mean ± SD.

	Diuripres® (*N* = 30)		Placebo (*N* = 30)	
Parameters	**Pre-run-in**	**Post-run-in**	**Pre-run in**	**Post-run in**
Age (years)	58.8 ± 4.3	–	59.1 ± 4.4	–
Body weight (kg)	79.7 ± 8.5	79.3 ± 8.4	80.3 ± 7.7	80.1 ± 7.9
Body mass index (kg/m^2)	25.2 ± 2.0	25.1 ± 1.9	25.5 ± 1.9	25.3 ± 1.8
Waist circumference (cm)	91.9 ± 6.5	89.9 ± 6.2	90.5 ± 5.9	89.9 ± 6.2
SBP (mmHg)	138.6 ± 5.5	138.3 ± 5.4	138.1 ± 5.4	137.8 ± 5.1
DBP (mmHg)	74.5 ± 3.9	74.2 ± 3.8	74.8 ± 3.4	74.0 ± 3.5

Abbreviations: DBP, diastolic blood pressure; *N*, number of individuals; SBP, systolic blood pressure.

TABLE 3 Diet composition (g/day) at enrollment and at the end of the clinical trial.

	Diuripres® (*N* = 30)		Placebo (*N* = 30)	
Parameters	**Baseline**	**Week 8**	**Baseline**	**Week 8**
Total energy (kcal/day)	1633 ± 102	1609 ± 95	1584 ± 93	1591 ± 103
Carbohydrates (% of total energy)	54.7 ± 2.4	53.0 ± 2.3	53.4 ± 2.5	52.6 ± 2.6
Proteins (% of total energy)	18.3 ± 1.3	18.5 ± 1.7	17.9 ± 1.4	18.3 ± 1.6
Animal protein (% of total energy)	10.6 ± 0.8	9.8 ± 0.7	10.3 ± 0.9	10.5 ± 0.7
Vegetal protein (% of total energy)	7.4 ± 0.5	7.6 ± 0.7	6.9 ± 0.5	7.0 ± 0.8
Total fats (% of total energy)	27.6 ± 2.1	27.7 ± 2.0	27.3 ± 1.8	28.1 ± 1.9
Saturated fatty acids (% of total energy)	7.9 ± 0.9	8.1 ± 0.8	8.2 ± 0.9	7.9 ± 1.0
MUFA (% of total energy)	12.5 ± 1.1	12.3 ± 0.9	12.6 ± 1.1	12.4 ± 1.0
PUFA (% of total energy)	6.5 ± 0.7	6.8 ± 0.8	6.6 ± 0.6	6.5 ± 0.7
Total dietary fibers (g/day)	19.9 ± 2.6	20.9 ± 2.9	19.6 ± 2.5	18.9 ± 2.7
Cholesterol (mg/day)	199 ± 14	186 ± 11	193 ± 12	195 ± 11

Note: Values are reported as mean ± SD.
Abbreviations: MUFA, monounsaturated fatty acids; *N*, number of individuals; PUFA, polyunsaturated fatty acids.

significant improvements in DBP, aortic BP, WC, HC, VAI, HDL-C, and hs-CRP in comparison with baseline (Table 4). Reductions in DBP, aortic BP, and hs-CRP were also significant compared to placebo (Table 4).

After correction for multiple testing, differences in anthropometric parameters and HDL-C from baseline were no more statistically significant, while between-group differences were still statistically significant. In particular, changes in DBP, aortic BP, and hs-CRP were −3.8 (95% CI −4.7 to −2.6 mmHg; $p < 0.05$), −5.2 (95% CI −6.9 to −2.1 mmHg; $p < 0.05$), and −0.03 (95% CI −0.05 to −0.01 mg/dL; $p < 0.05$), respectively.

3.2 | Safety analysis

All participants completed the clinical trial according to the study design (dropout rate = 0%). No treatment-emergent adverse event was reported nor laboratory abnormality occurred during the study.

4 | DISCUSSION

In the last decades, there has been a growing interest in natural compounds targeting multiple biochemical pathways (Cicero, Fogacci, et al., 2017; Krzemińska et al., 2022). This effort—together with a drive for innovative non-pharmacological treatments of hypertension—has recently resulted in remarkable advances in the field of CVD prevention (Cicero, Veronesi, & Fogacci, 2021).

The CONDOR study showed that the administration of a new dietary compound containing magnesium oxide and standardized dry extracts of orthosiphon, hawthorn, and hibiscus to individuals with high-normal BP or stage I hypertension led to significant decreases in BP and a number of metabolic biomarkers and indices of visceral adiposity, that are strongly related to insulin sensitivity. In effect, the usefulness of the individual components of Diuripres® to prevent CVD is supported by a large body of evidence acquired through both pre-clinical and clinical investigations.

Orthosiphon stamineus leaves contain several chemically active constituents (e.g., terpenoids: diterpenes and triterpenes, sterols and polyphenols: lipophilic flavonoids and phenolic acids) providing radical-scavenging activity toward the diphenylpicryihydrazyl radical and the inhibition of 15-lipoxygenase (Amzad Hossain & Mizanur Rahman, 2015). Moreover, lipophilic flavonoids from orthosiphon leaf enhance diuresis and sodium excretion by interacting with the adenosine A1 renal receptor (Adam et al., 2009; Yuliana et al., 2009); the final result is a reduction in BP levels, as also shown in humans, in the context of a clinical trial enrolling hypertensive individuals with

TABLE 4 Anthropometric and laboratory parameters in the study groups, expressed as mean ± SD.

	Diuripres® ($N = 30$)			Placebo ($N = 30$)		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Demographic and anthropometric parameters						
Body weight (kg)	79.3 ± 8.4	78.6 ± 8.1	78.5 ± 7.9	80.1 ± 7.9	79.7 ± 7.5	79.5 ± 7.1
Body mass index (kg/m^2)	25.1 ± 1.9	25.2 ± 1.7	25.4 ± 1.5	25.3 ± 1.8	24.9 ± 2.1	25.0 ± 1.7
Waist circumference (cm)	89.9 ± 6.2	87.5 ± 5.4	86.1 ± 4.2*	89.9 ± 6.2	89.8 ± 6.4	88.9 ± 5.9
Hip Circumference (cm)	97.2 ± 7.1	95.4 ± 6.8	93.2 ± 6.7*	95.5 ± 7.0	96.3 ± 6.6	95.3 ± 6.9
Waist-to-hip ratio	0.92 ± 0.13	0.92 ± 0.11	0.92 ± 0.12	0.94 ± 0.15	0.93 ± 0.11	0.93 ± 0.16
Index of central obesity	0.52 ± 0.08	0.51 ± 0.09	0.49 ± 0.07	0.53 ± 0.09	0.51 ± 0.13	0.50 ± 0.12
Visceral adiposity index	5.9 ± 0.9	5.7 ± 1.0	5.4 ± 0.6*	5.8 ± 0.7	5.9 ± 0.8	5.8 ± 0.9
Fat mass (%)	32 ± 3	31 ± 4	31 ± 2	33 ± 4	32 ± 4	32 ± 4
Lean mass (%)	66 ± 5	65 ± 6	65 ± 4	65 ± 6	67 ± 4	66 ± 5
Total body water (%)	51 ± 3	50 ± 3	49 ± 4	50 ± 4	51 ± 4	50 ± 3
Laboratory parameters						
Total cholesterol (mg/dL)	214.8 ± 12.2	216.2 ± 13.4	213.1 ± 14.1	213.2 ± 15.1	211.9 ± 14.3	209.8 ± 14.8
Triglycerides (mg/dL)	139.3 ± 18.4	136.8 ± 17.7	139.4 ± 19.8	136.3 ± 15.9	138.3 ± 21.1	141.1 ± 23.5
HDL-C (mg/dL)	48.2 ± 2.2	49.1 ± 2.3	50.2 ± 2.4*	47.9 ± 2.3	48.5 ± 3.1	47.6 ± 2.3
LDL-C (mg/dL)	138.8 ± 8.6	139.2 ± 8.8	136.5 ± 8.7	137.3 ± 8.9	135.8 ± 9.3	138.1 ± 8.1
FPG (mg/dL)	91.4 ± 3.6	90.1 ± 3.8	90.8 ± 3.9	92.1 ± 4.1	90.3 ± 3.9	92.6 ± 3.8
AST (U/L)	20.7 ± 2.8	21.2 ± 2.9	20.6 ± 2.7	22.5 ± 2.9	23.8 ± 3.1	22.9 ± 2.8
ALT (U/L)	21.5 ± 2.7	21.4 ± 2.9	21.3 ± 2.9	20.3 ± 2.8	21.0 ± 2.9	20.8 ± 2.7
gGT (U/L)	24.1 ± 3.1	24.3 ± 3.0	24.0 ± 3.3	23.1 ± 2.9	23.4 ± 2.7	24.1 ± 3.1
Serum uric acid (mg/dL)	5.4 ± 1.2	5.3 ± 1.1	5.1 ± 0.9	5.3 ± 1.2	5.4 ± 1.2	5.1 ± 1.4
eGFR (mL/min)	88.2 ± 4.3	85.9 ± 4.8	86.9 ± 4.7	85.7 ± 4.1	87.1 ± 4.3	84.3 ± 3.9
hs-CRP (mg/dL)	0.15 ± 0.09	0.13 ± 0.11	0.11 ± 0.08*,**	0.16 ± 0.11	0.17 ± 0.12	0.16 ± 0.07
Hemodynamic parameters						
SBP (mmHg)	138.3 ± 5.4	135.1 ± 5.7*	134.7 ± 5.6*,**	137.8 ± 5.1	135.8 ± 5.4	135.9 ± 5.3
DBP (mmHg)	74.2 ± 3.8	72.6 ± 3.9	71.1 ± 3.5*,**	74.0 ± 3.5	73.7 ± 3.4	74.9 ± 3.3
Pulse pressure (mmHg)	63.1 ± 3.3	63.0 ± 3.1	63.4 ± 2.9	62.8 ± 3.4	63.2 ± 3.5	63.3 ± 3.7
Aortic blood pressure (mmHg)	133.5 ± 4.8	131.6 ± 4.1	129.2 ± 4.2*,**	133.4 ± 4.9	132.9 ± 4.7	134.7 ± 4.9
Augmentation Index	20.7 ± 2.5	20.3 ± 2.8	21.4 ± 2.1	21.3 ± 2.1	20.8 ± 2.3	21.1 ± 2.3
Heart rate (bpm)	69.5 ± 4.2	69.1 ± 4.3	69.0 ± 4.4	68.1 ± 3.3	67.8 ± 4.1	67.3 ± 4.0
FMD	1.36 ± 0.26	1.37 ± 0.29	1.39 ± 0.23	1.34 ± 0.29	1.36 ± 0.23	1.35 ± 0.21

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; FPG, fasting plasma glucose; gGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
*$p < 0.05$ versus baseline.**$p < 0.05$ versus placebo [an analysis of variance (ANOVA) for repeated measures with two study factors: the within-subject factor (time: baseline, 4 weeks, and 8 weeks) and between-subject factor (intervention: Diuripres® and placebo) for paired data].

dyslipidemia who were already treated with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCB; Cicero et al., 2012).

Hawthorn dry extract has been shown to exert antihypertensive effect in vivo (Cloud et al., 2020) and preserve endothelial function from oxidative stress-induced damage in vitro (Wu et al., 2020; Xiyun & Yaofa, 2002). Moreover, dietary supplementation with hawthorn induces anti-inflammatory properties through the modulation of a number of cytokines with pro-inflammatory [Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)] and anti-inflammatory [Interleukin-10 (IL-10)] functions (Kmail et al., 2017; Nazhand et al., 2020).

Hibiscus improves vasodilation through the inhibition of calcium influx into vascular smooth muscle cells and increasing the excretion of sodium and chloride (Ajay et al., 2007; Alarcón-Alonso et al., 2012; Joven et al., 2014). Moreover, hibiscus anthocyanin delphinidin 3-sambubioside and cyanidin 3-sambubioside have been shown to competitively inhibit ACE and upregulate the endothelial nitric oxide (NO) synthase (NOS), definitely contributing toward a multifaceted

approach to BP management (Min et al., 2010; Parichatikanond et al., 2012; Xu et al., 2004).

The mild diuretic effect of ortosiphon and hibiscus partly explains why patients treated with Diuripres® experienced a mild but statistically significant decrease in WC and HC (but not in WC/HC ratio) and a mild (and not statistically significant) reduction in percentage body water content, while body weight did not change during the trial.

Finally, magnesium oxide is a major regulator of vascular tone and modulates the peripheral vascular resistance by enhancing relaxation responses and mitigating agonist-induced vasoconstriction (Dominguez et al., 2020). At molecular level, magnesium oxide acts as calcium antagonist, increases the synthesis of vasodilators (e.g., prostacyclin and NO), and inhibits vascular calcifications through the modulation of the transient receptor potential cation channel subfamily M member 7 (TRPM7; Piuri et al., 2021).

Thus, from a pharmacological point of view, the mechanisms of action of the single components of Diuripres® are different and potentially additive. On the other side, the single molecules per se seem to exert a significant BP-lowering effect only when taken at a high dosage and more times a day (Cicero et al., 2019): this could decrease patients' adherence to the treatment on the long-term (Choudhry et al., 2022). As a matter of fact, treatment adherence in CVD prevention remains a challenge for patients and healthcare providers, and lack of compliance is not only associated with a lower quality of life and poor health outcomes, but also has socio-economic impact and generates elevated costs to healthcare systems (Fuster et al., 2017). The polypill is expected to simplify the therapy by reducing the individual pill burden, which may improve adherence to treatments and decrease the risk of developing CV events in the long term (Fuster et al., 2017). Based on these assumptions, Diuripres® explicitly refers to the "quadpill concept," which has been recently coined for the antihypertensive drug therapies and describes that of a single pill combining four types of BP-lowering medications (with each medicine included at a quarter of the standard dose for hypertension; Bennett et al., 2017). Based on the conclusion of the QUARTET clinical trial, patients with hypertension who started therapy with a single pill composed of four low-dose medications achieved greater BP control than those who initiated with monotherapy (Chow et al., 2021). Similarly, dietary supplementation with Diuripres® is likely to be associated with greater benefits than its single components in individuals with high-normal BP or stage I hypertension. Finally, the BP decrease recorded with Diuripres® might be clinically relevant, since even small reduction in BP values (5 mmHg) has been associated with a CV event risk reduction of 10%, even in individuals with normal-high BP (Blood Pressure Lowering Treatment Trialists' Collaboration, 2021).

Despite the relevant findings and the practical implications, this study is not without limitations. We acknowledge the relatively small sample size, even though the study was powered for the primary outcome. Then, we did not sample information on socio-economic status of the enrolled subjects. Moreover, the run-in diet did not significantly modified anthropometric and BP level, presumably because we enrolled individuals with an overall correct diet at the baseline and because of the short duration of the dietary intervention. The FFQ questionnaire we used was not able to estimate the amount of water the individuals were taking during the study, and this is certainly another limitation that deserves to be acknowledged. Therefore, the relatively short follow-up does not clarify on the possible occurrence of adaptation phenomena, which however have never been documented before for the individual components of Diuripres®. We also acknowledge that the effect of the aluminum content in hibiscus extract was not accounted, even if—according to the findings of a recent comprehensive systematic review and meta-analysis (Ellis et al., 2022)—dietary supplementation with hibiscus is not likely to exert any adverse event at lower doses than 10 g/day (which is a much higher amount than that contained in Diuripres®). Due to performing multiple comparison analyses, it is possible that our results are at risk for a type I error. The absence of data on the effect of Diuripres® on pro-inflammatory cytokines and the renin-angiotensin system (RAS) and aldosterone production are further limitations of the study. However, this is the first clinical trial testing the effects of Diuripres® so that the preliminary and exploratory nature of the study limited the relevance of the application of an adjustment for multiple testing (Bender & Lange, 2001). Further long-term data sampled on larger patient samples is needed to confirm our preliminary observations on a limited number of efficacy parameters.

5 | CONCLUSIONS

In conclusion, the CONDOR study shows that 8-week treatment with a dietary supplement (Diuripres®) containing magnesium oxide, standardized dry extracts of orthosiphon (*Orthosiphon stamineus Benth*), hawthorn (*Crataegus curvisepala Lind.*), and hibiscus (*Hibiscus sabdariffa L.*) positively affects BP, vascular health, and a number of metabolic parameters in individuals with high-normal BP or stage I hypertension.

AUTHOR CONTRIBUTIONS

Federica Fogacci: Investigation; methodology; visualization; writing – original draft. **Daniela Degli Esposti:** Data curation; investigation; writing – review and editing. **Antonio Di Micoli:** Investigation; writing – review and editing. **Giulia Fiorini:** Investigation; writing – review and editing. **Maddalena Veronesi:** Investigation; writing – review and editing. **Claudio Borghi:** Supervision; writing – review and editing. **Arrigo Cicero:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; visualization; writing – original draft.

ACKNOWLEDGMENTS

The authors are sincerely grateful to all the volunteers who agreed to participate in the clinical trial.

FUNDING INFORMATION

Products were manufactured and provided by Neopharmed Gentili S. p.A. (Milano, MI, Italy), who also fully funded the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Neopharmed Gentili S.p.A. (Milano, MI, Italy) had no role in the design of the study; in the collection, analyses, and interpretation of data; in writing of the manuscript, and in the decision to publish the results.

DATA AVAILABILITY STATEMENT

Data supporting study's findings are available from the corresponding author with the permission of the University of Bologna and the sponsor.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all individuals involved in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fogacci, F., Degli Esposti, D., Di Micoli, A., Fiorini, G., Veronesi, M., Borghi, C., & Cicero, A. F. G. (2023). Effect of dietary supplementation with Diuripres® on blood pressure, vascular health, and metabolic parameters in individuals with high-normal blood pressure or stage I hypertension: The CONDOR randomized clinical study. *Phytotherapy Research*, *37*(10), 4851–4861. https://doi.org/10.1002/ptr.7951