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Impact of 10% thymoquinone-standardized *Nigella sativa* oily extract on 24-hour blood pressure profile and nocturnal dipping: a subgroup analysis of a pilot study in postmenopausal hypertensive women

Our recent pilot study, performed in postmenopausal women with a diagnosis of uncomplicated essential hypertension, treated with anti-hypertensive drugs, demonstrated that the 8-week administration of Nisatol® (provided by PharmExtracta S.p.A., Piacenza, Italy), a supplement containing 400 mg of a 10% thymoquinone-standardized *Nigella sativa* (NS) extract formulated with phospholipids and vitamin E to enhance active bioavailability and stability, significantly and dose-dependently reduced office blood pressure, cholesterol, weight, BMI and climacteric symptoms.¹ Our results confirmed the role exerted by NS extracts as antihypertensive, lipid-lowering, and anti-climacteric botanical mainly attributable to its bioactive compound thymoquinone.² However, limited data are available regarding its effects

on 24-hour blood pressure profiles and circadian blood pressure regulation, which are recognized as important predictors of cardiovascular risk.^{3, 4} The value of nutraceuticals and dietary lifestyle is fundamental in cardiovascular prevention.⁵ The present addendum therefore specifically describes the effects of NS supplementation on 24-hour ambulatory blood pressure monitoring (ABPM) parameters, including mean systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), and nocturnal dipping patterns. Our subgroup analysis concerns with 7 patients underwent 24-hour ABPM both at baseline (T0) and after 8 weeks (T2), being 4 patients treated daily with 800 mg/day of NS (group NS2), and 3 patients serving as untreated controls (Control Group). Institutional authorizations, methods, outcomes and statistical analysis are described in Supplementary Digital Material 1, Supplementary Text File 1. As shown in Figure 1 and in Supplementary Digital Material 2, Supplementary Table I, at baseline, mean 24-hour systolic and diastolic blood pressure (SBP/DBP) values were comparable between the two groups, with mean SBP ranging from 128-135 mmHg and DBP from 79-85 mmHg. After 8 weeks of treatment, treated patients experienced a reduction in 24-hour SBP and DBP, with values remained unchanged in control ones. The same trend was observed in daytime and nighttime averages, with significant reductions observed only in treated patients (Supplementary Digital Material 3: Supplementary Table II). Mean 24-hour heart rate, initially around 75-80 bpm, showed a consistent decrease in the NS2 group at T2 (-5 to -7 bpm on average), while no variations were observed in the control group. Analysis of

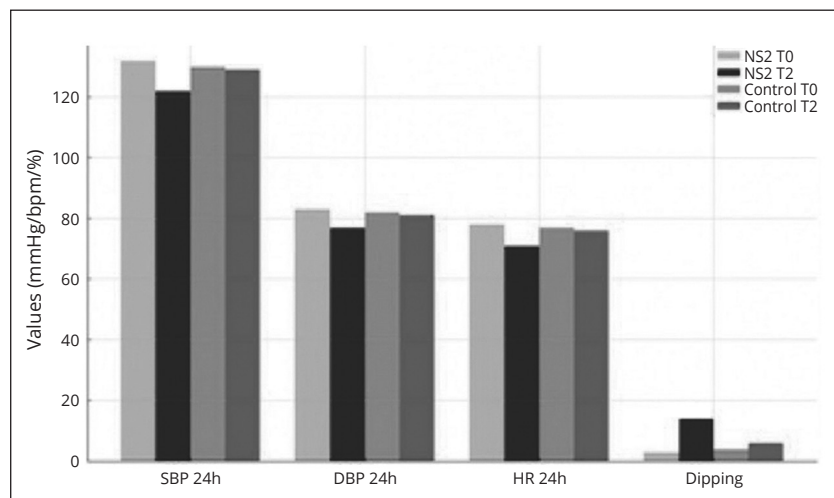


Figure 1.—24 h Ambulatory blood pressure monitoring (ABPM) results.

Statistical analysis of within-group changes (paired *t*-test) confirmed that in the NS2 group the reduction in mean 24-hour SBP reached statistical significance ($P \approx 0.047$), while the improvement in nocturnal dipping was highly significant ($P \approx 0.007$). The reductions in DBP and HR showed only a favorable trend without reaching statistical significance ($P = 0.46$ and $P = 0.056$, respectively). In contrast, no significant changes were observed in the control group across any of the parameters.

the circadian profile revealed a significant improvement in nocturnal dipping in the NS2 group. At baseline, most treated patients exhibited a blunted dipping profile (mean reduction <5%), while after 8 weeks the dipping values returned to a physiological range (10-20%). Notably, one among the treated patients showed a reverse dipping pattern at baseline, which normalized at T2, further supporting the favorable effect of supplementation on circadian BP rhythm.

Our findings suggest that NS supplementation may represent a useful complementary strategy in postmenopausal women with mild but uncontrolled hypertension despite ongoing pharmacological therapy. This is particularly relevant considering that suboptimal blood pressure control is a major determinant of hypertension-mediated organ damage (HMOD), a condition that reflects structural or functional injury to major organs and contributes to the continuum of cardiovascular risk.^{6, 7} Even in patients with only mildly elevated or non-target BP levels, the presence of HMOD has been associated with an increased risk of cardiovascular morbidity and mortality. An additional aspect highlighted in our subgroup is the improvement in nocturnal dipping. According to current evidence, the night-to-day BP ratio is an important predictor of outcomes, and individuals classified as nondippers or reverse dippers have a substantially higher risk of cardiovascular events compared with normal dippers.^{3, 8} Our results showed a normalization of dipping in the NS2 group, including one patient with baseline reverse dipping, suggesting a potential role of NS in restoring circadian BP physiology. Mechanisms underlying nocturnal hypertension and altered dipping include sympathetic overactivity, impaired baroreflex sensitivity, salt sensitivity, plasma volume expansion, and sleep disturbances such as obstructive sleep apnea.⁹ Currently, no selective pharmacological treatment is available to specifically address nocturnal BP alterations, and therapeutic options remain limited to indirect approaches, such as bedtime dosing of antihypertensive drugs, sodium restriction, or OSA treatment. In this context, natural compounds such as NS, above when in form of highly standardized product, could provide an innovative, safe, and well-tolerated adjunctive approach.¹⁰ Its potential target population may not only include women with suboptimal BP control on pharmacological therapy, but also those with high-normal BP values who are not yet candidates for drug treatment. This early intervention could help to improve nocturnal BP control, preserve circadian BP physiology, and possibly delay the onset of pharmacological therapy. Although our results demonstrated in postmenopausal women significant reduction of 24-hour, daytime, and nighttime SBP, decrease in heart rate and DBP, and normalization of the nocturnal dipping pattern, including the correction of one case of reverse dipping, these preliminary observations deserve confirmation in larger, randomized controlled trials. Future studies should focus on whether early use of *Nigella sativa* may help to improve nocturnal BP control and prevent the progression of HMOD, particularly in hypertensive patients with altered circadian BP profiles.

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Conflicts of interest

Francesco Di Pierro is the Scientific and Research Director of Pharmextracta. The other authors declare no conflicts of interest.

Authors' contributions

Conceptualization: Barbara Pala and Giuliano Tocci; methodology, Barbara Pala, Giulia Nardoiani and Giuliano Tocci; formal analysis: Barbara Pala and Giulia Frank; investigation: Barbara Pala, Giulia Nardoiani and Giuliano Tocci; data curation: Barbara Pala and Giuliano Tocci; writing—original draft preparation: Barbara Pala, Laura Di Renzo, Paola Gualtieri, Giuliano Tocci, Francesco Di Pierro, Nicola Zerbinati; writing—review and editing, all authors. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Institutional authorizations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Calabria Region Central Area Section (protocol no. 97, 20 April 2023). Written informed consent was obtained from all subjects involved in the study.

Ambulatory blood pressure monitoring

ABPM was performed using validated oscillometric devices (Mobil-O-Graph PWA Monitor, I.E.M. GmbH, Germany), in accordance with current European Society of Hypertension guidelines.¹ Blood pressure was recorded every 15 minutes during daytime (06:00–22:00) and every 30 minutes during nighttime (22:00–06:00). Mean systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), and the nocturnal dipping percentage were calculated at baseline and at 8 weeks. All ABPM recordings were performed and analyzed by cardiologists at the Hypertension Unit of Sant' Andrea Hospital, Sapienza University of Rome, using validated devices.

Outcomes

The primary outcome of this analysis was the change in mean 24-hour SBP after 8 weeks of supplementation. Secondary outcomes included changes in mean 24-hour DBP, HR, and dipping status.

Statistical analysis

Continuous variables are presented as mean \pm SD. Differences between T0 and T2 within each group were assessed using paired t-tests. Given the small sample size, results should be interpreted as exploratory and hypothesis-generating. Statistical significance results was defined with $p < 0.05$.

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SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Ambulatory blood pressure monitoring in patients treated with 800 mg/day of *Nigella sativa* oil and in control ones.

	NS2 - T0 (n=4)	NS2 - T2 (n=4)	Control - T0 (n=3)	Control - T2 (n=3)
SBP 24h (mmHg)	132 ± 5	122 ± 4*	130 ± 4	129 ± 5
DBP 24h (mmHg)	83 ± 3	77 ± 3	82 ± 3	81 ± 3
HR 24h (bpm)	78 ± 4	71 ± 3*	77 ± 5	76 ± 4
Dipping (%)	3 ± 2	14 ± 3	4 ± 2	6 ± 2

*Twenty-four-hour ambulatory blood pressure monitoring (ABPM) results at baseline (T0) and after 8 weeks (T2) in patients treated with Nigella sativa 800 mg/day (NS2, n=4) and in controls (n=3). Values are expressed as mean ± SD. *p<0.05.*

SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table II.—Daytime and nighttime blood pressure monitoring in patients treated with 800 mg/day of *Nigella sativa* oil and in control ones.

	NS2 - T0 (n=4)	NS2 - T2 (n=4)	Control - T0 (n=3)	Control - T2 (n=3)
SBP 24h (mmHg) daytime	132 ± 5	122 ± 4*	130 ± 4	129 ± 5
DBP 24h (mmHg) daytime	83 ± 3	77 ± 3	82 ± 3	81 ± 3
SBP 24h (mmHg) Nighttime	128 ± 5	105 ± 4*	125 ± 5	122 ± 6
DBP 24h (mmHg) nighttime	79 ± 4	70 ± 3	79 ± 3	76 ± 3

*Daytime and nighttime blood pressure monitoring results at baseline (T0) and after 8 weeks (T2) in patients treated with Nigella sativa 800 mg/day (NS2, n=4) and in controls (n=3). Values are expressed as mean ± SD. *p<0.05.*