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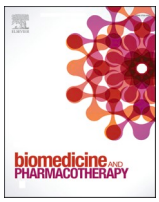

Effects of CBD supplementation on ambulatory blood pressure and serum urotensin-II concentrations in Caucasian patients with essential hypertension: A sub-analysis of the HYPER-H21-4 trial

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ABSTRACT

HYPER-H21–4 was a randomized crossover trial that aimed to determine if cannabidiol (CBD), a non-intoxicating constituent of cannabis, has relevant effects on blood pressure and vascular health in patients with essential hypertension. In the present sub-analysis, we aimed to elucidate whether serum urotensin-II concentrations may reflect hemodynamic changes caused by oral supplementation with CBD. The sub-analysis of this randomized crossover study included 51 patients with mild to moderate hypertension that received CBD for five weeks, and placebo for five weeks. After five weeks of oral CBD supplementation, but not placebo, serum urotensin concentrations reduced significantly in comparison to baseline (3.31 ± 1.46 ng/mL vs. 2.08 ± 0.91 ng/mL, $P < 0.001$). Following the five weeks of CBD supplementation, the magnitude of reduction in 24 h mean arterial pressure (MAP) positively correlated with the extent of change in serum urotensin levels ($r = 0.412$, $P = 0.003$); this association was independent of age, sex, BMI and previous antihypertensive treatment (β ± standard error, 0.023 ± 0.009, $P = 0.009$). No correlation was present in the placebo condition ($r = -0.132$, $P = 0.357$). In summary, potent vasoconstrictor urotensin seems to be implicated in CBD-mediated reduction in blood pressure, although further research is needed to confirm these notions.

1. Introduction

Arterial hypertension is a major cardiovascular risk factor contributing to the global all-cause mortality [1]. Yet, adherence to antihypertensive drugs is commonly very low, thus resulting in suboptimal outcomes. In addition to antihypertensive medications, in the recent years the effects of dietary changes and food supplements on blood pressure management have come under the spotlight in recent years.

Cannabidiol (CBD) is a non-intoxicating constituent of *Cannabis sativa* L., a plant used for centuries in various cultural and religious rituals [2]. CBD belongs to the group C21 (C22 for carboxylated forms) of terpenophenols, and the biosynthesis occurs in the glandular trichomes present primarily on female flowers [3]. Accumulating data from both basic and clinical research has shown that CBD offers multidirectional properties including antioxidant, anti-inflammatory, immunomodulatory, anticonvulsant, neuroprotective, anti-proliferative and many others [4–6]. Hence, it was concluded that CBD might hold significant therapeutic potential, which eclipsed in registration of Epidiolex® (GW Pharmaceuticals, UK), the first drug to exclusively use CBD as an active ingredient, in the treatment of severe drug-resistant epilepsy [7]. Lately, a great deal of attention was aimed at elucidating cardiovascular effects of this molecule [8]. Specifically, early preclinical reports suggested that CBD can elicit multiple cardiovascular effects such as cardiac contractility, vasodilation, vascular inflammation and blood

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pressure [9–11]. Nonetheless, it has to be addressed that these effects were not consistently demonstrated, even when replicated in the same species. Mechanisms involved in the observed hemodynamic effects of CBD seem to be pleiotropic and include effects on cannabinoid receptors (CB_1 and CB_2), modulation of endocannabinoids, and various biologically active compounds that may affect cardiovascular system function.

Urotensin-II, a pleiotropic undecapeptide expressed in endothelial cells, macrophages, and multiple other cells, is considered one of the most powerful vasoconstrictors [12]. Accumulating data suggests that urotensin-II may induce cardiac fibrosis, cardiomyocyte hypertrophy, and vascular remodeling [13,14]. Moreover, serum urotensin-II levels seem to be elevated in patients with essential hypertension, atherosclerosis, and coronary artery disease [15–17].

As the effects of CBD on blood pressure and vascular health have so far been poorly elucidated in humans, we recently conducted HYPER-H21–4, a randomized, placebo-controlled and crossover trial. The primary aim of the trial was to determine whether 5-week administration of CBD supplement would reduce ambulatory BP and arterial stiffness in patients with essential hypertension. Specifically, we used DehydraTECH™2.0 CBD, a patented CBD formulation developed to increase the bioavailability of CBD [18].

Considering the involvement of urotensin-II in vascular remodeling and pathophysiology of essential hypertension, in the present study, we aimed to establish if 5-week administration of CBD will affect serum urotensin-II concentrations and whether changes in ambulatory blood pressure will be reflected in changes of urotensin-II serum levels.

2. Methods

2.1. Study design and participants

The present study represents a sub-analysis of the HYPER-H21–4, a randomized, placebo-controlled and crossover trial that was conducted in the period from December 2021 to April 2022. The details concerning the protocol of this trial has been reported elsewhere [18]. The study was conducted at the Department of Integrative Physiology, University of Split School of Medicine, Split, Croatia in accordance with the Declaration of Helsinki and was reviewed by the Ethical Committee of the same institution. Prior to study enrolment, participants were obliged to sign informed consent. The trial itself was registered at ClinicalTrials.gov (ID: NCT05346562). The trial was sponsored by Lexaria Bioscience Corp. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

For this sub-analysis, based on sample size calculation needed to demonstrate difference in urotensin-II serum levels (44 participants, with α 0.05 and β 0.1) we randomly selected 51 patients with Grade 1 or Grade 2 hypertension (defined by the latest European Society of Cardiology guidelines for management of hypertension) [19]. Inclusion criteria also included age 40–70 years and body mass index (BMI) between 18.5 and 35 kg/m^2.

Exclusion criteria were secondary hypertension, treatment with hypertensive medications other than ACE inhibitors, diuretics and calcium channel blockers, smoking (including cannabis), use of any CBD-containing supplements, significant cardiac, renal or liver disease, diabetes mellitus, gout, chronic gastrointestinal disease, significant psychiatric disorders, and diagnosis/ history of disorders associated with seizures. The presence of inclusion and exclusion criteria was assessed using a medical screening questionnaire during a clinical examination and baseline blood chemistry findings. In addition, serious adverse events and excessive increase in liver enzymes (as discussed in detail in the protocol) during any point in trial led to immediate exclusion from the trial.

The safety of CBD supplementation was continuously monitored during the whole course of the trial. Subjects were instructed to contact a study team member in case of adverse event development. The principal investigator and two study investigators holding a medical degree monitored and tabulated adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0 [20]. The study was to terminate if more than 20% of patients developed serious adverse events.

2.2. Interventions, trial visits and follow-up

Participants were randomized in a 1:1 fashion to one of two treatment sequences: Placebo then DehydraTECH™2.0 CBD ("A then B") or DehydraTECH™2.0 CBD then placebo ("B then A"). In the A then B intervention arm, patients received placebo capsules for 5 weeks and were then switched to 5 weeks of oral CBD supplementation. The dosage ranged from 225 to 300 mg in the first 2.5 weeks, and 375–450 mg in the next 2.5 weeks (based on sex and weight of the participants as discussed in the protocol) (Supplementary Figure 1) [18]. On the other hand, patients in the B then A intervention arm received CBD for five weeks in the aforementioned dosages, followed by a 2-week washout and 5 weeks of placebo. The capsule manufacturing process (CBD and matching placebo capsules) was described in detail in the study protocol [18].

The baseline visit consisted of thorough anamnesis and detailed physical examination. Basic anthropometric measurements were assessed using measuring tape (GIMA SpA, Bologna, Italy), an altitude meter (Seca, Birmingham, UK) and bioimpedance scale Tanita DC-360 S (Tanita, Tokyo, Japan). Based on these measurements, BMI and waist to hip ratio were calculated as per standard formulas.

Ambulatory blood pressures were obtained using Schiller BR-102 plus PWA (Schiller AG, Baar, Switzerland). According to recommendations of the contemporary guidelines, a minimum of 70% usable BP recordings were required for a valid ambulatory BP measurement session [19]. The analysis was performed by two independent study investigators holding medical degree who were blinded to the intervention arm, following Casadei method [21]. Data for pulse wave analysis was obtained using the same monitoring system. Ambulatory blood pressures and blood samples were obtained at 4 instances: at the start and at the end of each dosing period (CBD or Placebo).

Blood samples for baseline laboratory and serum urotensin-II were obtained from the cubital vein using a sterile disposable needle. Part of the sampled blood was immediately analyzed, whereas part of the sample was aliquoted and stored on − 80 °C for subsequent analysis of biomarkers, including urotensin-II. All blood samples were analyzed using standard operating protocols in the same accredited institutional biochemical laboratory by an experienced biochemist who was unaware of the participant allocation. Serum urotensin-II concentrations (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) were determined by ELISA. The sensitivity of the urotensin-II assay was 0.06 ng/mL with a linear range of 0.06–8.2 ng/mL. Furthermore, cross-reactivity with endogenous human urotensin-II was 100% with intra-assay and inter-assay coefficients of variability of $< 10\%$ and $< 15\%$, respectively.

2.3. Statistical analysis

SPSS statistics (version 29.0, IBM, Chicago, IL, USA) and Prism 6 for Windows® (version 9.4.1, GraphPad, La Jolla, CA, USA) were used for all data analysis and graphical representation of data.

Shapiro-Wilk test was used to assess the normality of data distribution. Mean and SD, mean and SEM (with reported 95% CI), and median (interquartile range) was used for qualitative data, depending on data distribution. Qualitative data were expressed as a whole number and percentage Quantitative variables were compared with Student's t-test or Mann-Whitney U test, as deemed appropriate, whereas qualitative data were compared using the chi-squared test. In order to establish the presence of urotensin-II serum concentration and to explore the influence of ambulatory MAP with respect to treatment period (CBD or placebo), we employed repeated measure ANOVA. The variable Δ_{CBD}Urotensin, defined as the difference between serum urotensin-II

concentration at the end of the CBD dosing period and serum urotensin-II concentration at the start of the CBD dosing period, was introduced. Furthermore, Δ_{CBD}MAP, a variable defined as difference between MAP at the end of CBD dosing period and MAP at the start of the CBD dosing period, and corresponding $\Delta_{Placebo}$MAP, have also been introduced. To examine the potential correlation between serum urotensin-II levels, Δ_{CBD}Urotensin and Δ_{CBD}MAP, we used Pearson's correlation coefficient. The r correlation coefficient (rho) and two-tailed significance (p) values were reported in that analysis. Finally, multiple linear regression analysis was used to determine whether association between Δ_{CBD}Urotensin and Δ_{CBD}MAP is independent of age, sex, BMI and previous antihypertensive treatment. Multicollinearity in the linear regression analysis has been assessed using the variance inflation factor (VIF). Significance was set at $p < 0.05$ for all comparisons.

3. Results

The average age of the studied population was 55.8 ± 7.1 years, 56.9% were male participants, and all patients were of Caucasian descent. No significant differences in baseline characteristics were found between subgroups of patients that were previously treated with antihypertensive medications, and those who weren't. The baseline characteristics of the studied population were delineated in Table 1.

Following 5-weeks of oral CBD supplementation, serum urotensin-II concentrations reduced significantly compared to baseline (3.31 ± 1.46 ng/mL vs. 2.08 ± 0.91 ng/mL, $P < 0.001$). On the other hand, following five weeks of placebo, no such reduction was observed (3.30 ± 1.45 ng/mL vs. 3.27 ± 1.47 ng/mL, $P = 0.170$) (Fig. 1).

In accordance with the above-noted reduction in serum urotensin-II concentrations, we demonstrated that average 24 h MAP significantly reduced after five weeks of oral CBD (Δ_{CBD}MAP = 4.14 ± 0.69 mmHg, $P < 0.001$), but not after 5-week placebo administration ($\Delta_{PLACEBO}$MAP = -1.46 ± 0.92 mmHg (95%CI −3.73 to 0.71 mmHg), $P = 0.354$) (Fig. 2). The observed reduction was not dependent on hypertension grade (F = 2.73, $P = 0.077$). Changes in systolic and diastolic BP are presented in Supplementary figure 2.

Pearson's correlation coefficient analyses revealed that the change in MAP (Δ_{CBD}MAP) was positively correlated with the change in serum urotensin-II levels (Δ_{CBD}Urotensin; r = 0.412, $P = 0.003$; Fig. 3). Furthermore, multiple linear regression analysis demonstrated that such correlation was independent of age, sex, BMI and previous treatment with antihypertensive drugs (β ± standard error, 0.023 ± 0.009, $P = 0.009$). On the other hand, no correlation was observed between baseline urotensin-II concentrations and Δ_{CBD}MAP (r = −0.132, $P = 0.357$), thus indicating that baseline urotensin-II concentration does not predict the extent of MAP change following chronic CBD supplementation. There were no relationships in the placebo condition.

4. Discussion

The present sub-analysis of the HYPER-H21–4 trial indicates that urotensin-II, a potent vasoconstrictive peptide, may be involved in CBD-mediated hemodynamic effects. Specifically, we demonstrated that urotensin-II serum concentrations reduced in concordance with the reduction of ambulatory BP after five weeks of oral CBD supplementation, and that such correlation is independent of age, sex, BMI or previous antihypertensive treatment. However, baseline urotensin-II concentrations did not herald the reduction in MAP. It is also worth mentioning that MAP change was independent of the degree of hypertension. To the best of our knowledge, this is the first study in which the dynamic of urotensin-II serum concentrations, and its association with BP, has been explored in the setting of chronic oral CBD supplementation.

The hemodynamic effects of CBD - the major non-intoxicating compound of cannabis - have been debated. In fact, most studies in animal models yielded rather disappointing results, with CBD-induced hemodynamic consequences being either modest or inconsistent in controlled environments, whereas studies in normotensive individuals failed to show benefit in terms of BP reduction. However, multiple authors reported significant hemodynamic effects of CBD in various stressful conditions, in both animal and human models. For instance, a meta-analysis reported that administration of CBD has no effect on BP or heart rate (HR) under control conditions, yet it reduces both HR and BP in stressful conditions [22]. It is nonetheless worth mentioning that studies from which the meta-analysis was comprised of mostly assessed the effects of acute CBD dosing (chronic dosing was evaluated in 4 studies in total). Conversely, Remiszewski et al. recently demonstrated that chronic administration of CBD did not lead to reduction in BP in a model of primary and secondary hypertension in rats, regardless of the fact that significant CBD-induced effects on the cardiac and plasma endocannabinoid systems, lipid metabolism and oxidative stress were observed [23]. On the other hand, Sadowska et al. showed that CBD may ameliorate monocrotaline-induced pulmonary hypertension in rats by reducing right ventricular systolic pressure and improving blood oxygen saturation [24]. Cardioprotective effects of CBD were demonstrated on a rat model of aluminum phosphide poisoning [25]. Specifically,

Table 1
Baseline characteristics of patients.

Parameter	Total (n = 51)	Treated hypertension (n = 26)	Untreated hypertension (n = 25)	P
Age, years	55.8 ± 7.1	56.2 ± 7.6	55.4 ± 6.9	0.713*
Male sex, n (%)	29 (56.9)	16 (61.5)	13 (52.0)	0.527†
Body mass index, kg/m^2	28.2 ± 3.3	28.1 ± 3.3	28.3 ± 3.4	0.938*
Waist-to-hip ratio	0.94 ± 0.08	0.94 ± 0.09	0.94 ± 0.07	0.947*
Total cholesterol, mmol/L	5.7 ± 1.0	5.7 ± 1.1	5.7 ± 0.9	0.868*
LDL-C, mmol/L	3.5 ± 0.9	3.5 ± 1.0	3.5 ± 0.8	0.899*
HDL-C, mmol/L	1.4 (1.2–1.7)	1.4 (1.1–1.7)	1.4 (1.2–1.8)	0.910‡
Triglycerides, mmol/L	1.3 (0.9–1.8)	1.4 (0.9–2.5)	1.3 (1.1–1.7)	0.409‡
Fasting blood glucose, mmol/L	5.1 (4.8–5.6)	5.2 (4.9–5.5)	5.2 (4.8–5.8)	0.770‡
Antihypertensive therapy, n (%)				
ACEi		14 (53.8)	0 (0)	N/A
ACEi + CCB		9 (34.6)	0 (0)	N/A
ACEi + diuretic		3 (11.5)	0 (0)	N/A
Hypertension grade§, n (%)				
Grade 1	45 (88.2)	23 (88.5)	22 (88.0)	0.959
Grade 2	6 (11.8)	3 (11.5)	3 (12.0)	
Baseline BP				
24 h MAP, mmHg	101.9 ± 8.5	102.3 ± 8.1	101.4 ± 9.0	0.701*
24 h SBP, mmHg	130.2 ± 10.1	130.7 ± 8.0	129.6 ± 12.1	0.703*
24 h DBP, mmHg	79.3 ± 7.5	78.5 ± 6.8	80.1 ± 8.2	0.444*
PWV, m/s	8.3 ± 1.1	8.3 ± 1.0	8.2 ± 1.2	0.761*
cAIx@75bpm, %	30.2 ± 6.7	28.7 ± 5.8	31.8 ± 7.3	0.106*

Data is presented as mean (SD), median [interquartile range], n (%). * Student's t-test for independent samples, † chi-squared test ‡ Mann-Whitney U test § According to 2018 ESC/ESH Guidelines for the management of arterial hypertension (14). Grade 1 indicates systolic blood pressure of 140–159 and/or diastolic of 90–99 mmHg, whereas Grade 2 indicates systolic blood pressure of 160–179 and/or diastolic of 100–109 mmHg (office values). LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACEi, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; cAIx@75bpm, central augmentation index at 75 bpm

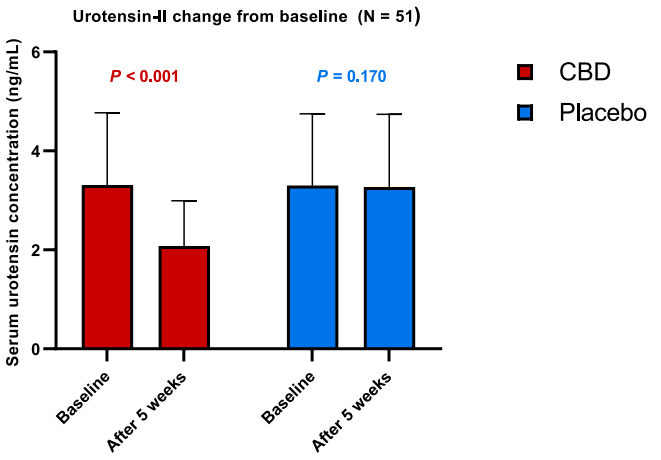

Fig. 1. Comparison between changes in serum urotensin-II concentration during CBD period and during Placebo period. Abbreviations: CBD: cannabidiol. Data are presented as mean ± SD. Data were analyzed using repeated measure ANOVA and post-hoc paired samples t-test were employed.

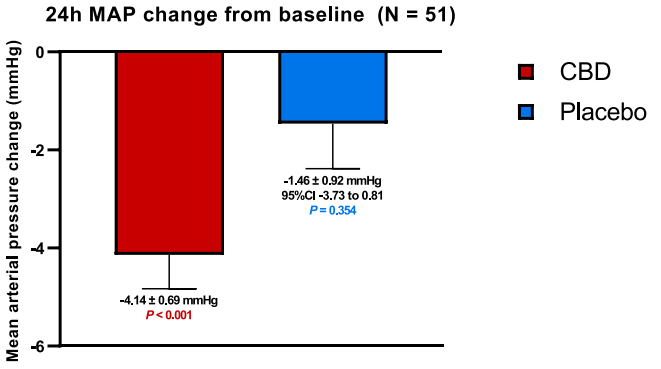

Fig. 2. Changes in MAP during CBD period and Placebo period. The red column indicates average change in MAP after 5 weeks of CBD dosing (in comparison to baseline MAP), the blue column indicates average change in MAP after 5 weeks of Placebo. Abbreviations: MAP: mean arterial pressure; CBD: cannabidiol. Data are presented as mean ± SEM. Data were analyzed using repeated measure ANOVA.

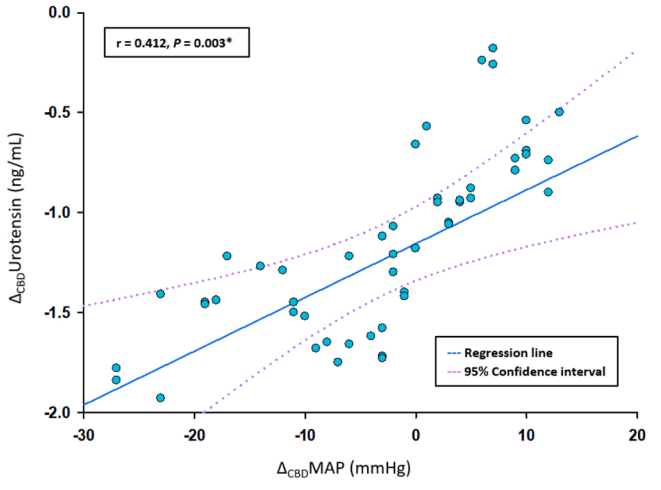

Fig. 3. Correlation between Δ_{CBD}Urotensin and Δ_{CBD}MAP (N = 51). Abbreviations: r: correlation coefficient; MAP: mean arterial pressure; CBD: cannabidiol *Pearson's correlation coefficient.

Hooshangi et al. showed that CBD restored mitochondrial function and ATP levels whilst decreasing oxidative damage, thus preventing cardiomyocytes from entering the apoptotic stage.

So far, only several small-scale studies explored CBD-mediated hemodynamic effects in humans. In a randomized trial (n = 26) CBD diminished mean arterial pressure after acute dosing without affecting ambulatory BP following six days of repeated dosing in healthy and normotensive individuals [26]. The same authors reported improved flow-mediated dilation and reduced arterial stiffness after repeated dosing [26]. Furthermore, Arout et al. showed in a randomized, placebo-controlled trial that CBD diminished systolic but not diastolic BP in comparison to placebo during the cold pressor test, whereas a randomized crossover study demonstrated that CBD reduces systolic BP and blunts BP in response to the cold pressor test [27,28]. In our previous study, using a similar formulation as DehydraTECH™2.0 CBD, we demonstrated attenuation of mean arterial pressure following acute dosing [29]. Accordingly, in a recent pharmacogenetic study (n = 24) we demonstrated that DehydraTECH™2.0 CBD reduced diastolic BP more than standard CBD formulation following acute dosing [30]. It is worth noting that a particular problem in the assessment of CBD-mediated hemodynamic effects is the abundance of possible CBD effector arms. Specifically, apart from cannabinoid receptors (for which CBD has low affinity), CBD may produce anti-inflammatory and antioxidant effects, but also affect the activity endocannabinoids, and many other biologically active compounds as well, such as, adenosine, dopamine, and serotonin. Finally, the results of recently conducted HYPER-H21–4, a randomized, placebo-controlled and crossover trial, suggest that chronic CBD administration reduces ambulatory BP in hypertensive patients [31]. We recently discussed that possible basis for CBD-mediated BP reduction might result from an interaction between CBD and the sympatho-chromaffin system, as evidenced by concomitant reduction in serum catestatin levels, and the fact that the extent of BP reduction was heralded by baseline catestatin concentrations [32]. Namely, catestatin is an established inhibitor of catecholamine secretion that seems to be implicated in pathophysiology of hypertension [33,34]. In view of the fact that most studies failed to demonstrate the hypotensive effect of CBD unless in the acute/stress settings, it is plausible that the effect that we observed in the present study is in part owing to from specific form of CBD formulation used, i.e. DehydraTECH™2.0 CBD.

In consideration of urotensin-II potent vascular effects, multiple authors explored the role of this peptide in the setting of hypertension. It was consistently shown that urotensin-II serum levels were higher in patients with hypertension [35–38]. Furthermore, Sondermeijer et al. reported dose-dependent vasodilator response in normotensive subjects, but dose-dependent vasoconstrictor response in hypertensive patients indicating that the vasodilatory actions of urotensin-II might depend on the condition of the endothelium [39]. However, a recent prospective study that included around 2000 normotensive individuals demonstrated that plasma urotensin-II levels were not associated with the risk of incident hypertension during a 5-year follow-up. In this regard, it also needs to be addressed that urotensin-II is a pleiotropic peptide. Specifically, various reports indicate that urotensin-II is implicated in the pathogenesis of atherosclerosis, hypertension, metabolic syndrome, liver cirrhosis, chronic kidney disease, and many others. Accordingly, serum urotensin-II levels have been elevated in these conditions [15–17, 40,41]. Svistunov et al. discussed that such pleiotropic effects could be explained by urotensin-II interaction with G protein-coupled receptor 14 (GPR 14), which can yield pro-fibrotic and pro-inflammatory effect, cell proliferation, induce insulin resistance and stimulate cardiac hypertrophy [42]. The interaction between urotensin-II and aberrant inflammatory response in the cardiovascular system requires particular attention. Specifically, urotensin-II was shown to induce the expression and secretion of ICAM-1 and VCAM-1 and induce monocyte chemotaxis in the context of vascular injury through the RhoA/Rho kinase pathway [42]. Furthermore, urotensin-II is not expressed in healthy coronary

arteries, whereas high levels of UII are found in plaques in patients with atherosclerosis, mainly arising from endothelial cells and macrophages [43]. On the other hand, urantide, an antagonist of the urotensin-II receptor, has been shown to protect against atherosclerosis in a rat model [44]. Overall, considering the eclectic nature of CBD, and only moderate correlation between serum urotensin-II and BP, we argue that multiple other mechanisms, such as changes in metabolic and inflammatory pathways, may also alter urotensin-II serum levels in this setting.

There are several noteworthy limitations of the present study. First, this was a single center study in which we included only Caucasian patients with essential hypertension. Hence, considering the variability of hypertensive phenotypes between different populations, the results of this analysis may not be pertinent to other populations. Furthermore, we did not include patients with severe hypertension. Moreover, there is no sufficient data to confirm that serum urotensin-II levels reflect its end-organ activity, and thus, it remains elusive whether the observed association between urotensin-II and BP response is a consequence of CBD-mediated action (that could in part explain the hypotensive effects of CBD formulation) or change in urotensin-II merely accompanies the reduction in BP. Finally, in the present study we used DehydraTECH™2.0 CBD, and no other formulations of CBD as comparators, which limits us from inferring whether our results are applicable to other CBD formulations. On the other hand, the strength of the present study lies in the fact that our population was comprised of individuals that were devoid of other conditions that might affect urotensin-II levels, such as diabetes mellitus, chronic illnesses and metabolic syndrome, and that we measured ambulatory BPs, which were shown to reflect the real state more reliably than the office BP. In addition, CBD dosing period was sufficiently long to reflect chronic and steady-state effects of CBD supplementation.

To summarize, although evidence concerning the hemodynamic effects of CBD is weak, the sub-analysis of the HYPER-H21–4 trial implies that urotensin-II could partially explain the hypotensive effects of DehydraTECH™2.0 CBD formulation. The major finding in this regard is concomitant reduction in urotensin-II serum concentrations and ambulatory BP. Nevertheless, considering the pleiotropic nature of urotensin-II, alongside the fact that only a modest correlation was observed between serum urotensin-II and ambulatory BP, there might be multiple other CBD-mediated mechanisms that contributed to the reduction in urotensin-II serum levels, such as inflammation and redox balance.

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CRediT authorship contribution statement

Marko Kumric: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Goran Dujic:** Visualization, Investigation, Formal analysis, Writing – original draft. **Josip Vrdoljak:** Visualization, Investigation, Formal analysis, Writing – original draft. **Daniela Supe-Domic:** Visualization, Investigation, Formal analysis, Writing – original draft. **Nada Bilopavlovic:** Visualization, Investigation, Formal analysis, Writing – original draft. **Kresimir Dolic:** Visualization, Investigation, Formal analysis, Writing – original draft. **Zeljko Dujic:** Conceptualization, Funding acquisition, Resources, Project administration, reviewing and editing editing of the manuscript. **Josko Bozic:** Conceptualization, Funding acquisition, Resources, Project administration and reviewing and editing of the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115016.

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