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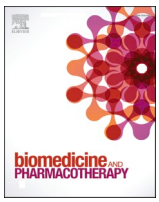

CBD supplementation reduces arterial blood pressure via modulation of the sympatho-chromaffin system: A substudy from the HYPER-H21-4 trial

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ABSTRACT

Data concerning the effects of cannabidiol (CBD) on blood pressure (BP) is controversial. HYPER-H21–4 was a randomized, placebo-controlled, crossover trial which sought to elucidate if 5-week administration of CBD will reduce BP in hypertensive patients. In the substudy of this trial, we aimed to establish the mechanistic background of CBD-induced BP reduction. Specifically, we explored the dynamic of catestatin, a sympathoinhibitory peptide implicated in the pathophysiology of hypertension. In the present analysis, 54 patients with Grade 1 hypertension were included. 5-week administration of CBD but not placebo reduced serum catestatin concentration in comparison to baseline (13.50 [10.85–19.05] vs. 9.65 [6.37–12.26] ng/mL, $p < 0.001$). Serum catestatin levels at the start of the treatment period demonstrated a negative correlation with the extent of reduction in mean arterial pressure ($r = -0.474$, $p < 0.001$). Moreover, the extent of change in catestatin serum levels showed a strong correlation with the extent of mean arterial pressure reduction ($r = 0.712$, $p < 0.001$). Overall, the results of the present study imply that the antihypertensive effects of CBD may be explained by its interaction with the sympatho-chromaffin system, although further research is warranted.

1. Introduction

It has been well-established that arterial hypertension constitutes a significant risk factor that portends cardiovascular mortality and morbidity [1]. However, the pathophysiology of primary hypertension has yet to be elucidated, even though a large body of evidence on the topic exists. In recent years, a particular focus was placed on the role of sympathetic nervous system (SNS) dysfunction in the development of primary hypertension [2,3]. Exploration of this interconnection has even been clinically challenged in the form of renal sympathetic denervation and baroreflex activation therapy, yielding promising success in the initial studies [4,5]. However, more recent randomized trials [6] had somewhat disappointing results, as these methods failed to demonstrate clear benefits, thus implying that there are more pieces to the puzzle.

Apart from the device-based and pharmacological treatments aimed at blood pressure reduction, multiple research groups also shed light on dietary and lifestyle changes that may serve the purpose as well [7]. In this regard, it has been demonstrated by multiple authors that cannabidiol (CBD), a non-intoxicating and well-tolerated constituent of cannabis, has distinct effects on cardiovascular regulation [8]. Specifically, it was shown that CBD might affect blood vessel tone, vascular inflammation, blood pressure, and cardiac contractility [9]. The mechanistic background of these observations seems to be complex and to include interaction with receptors other than cannabinoid receptors, but also indirect actions exerted through modulation of endogenous mediators' metabolism [10]. Yet, as most conclusions about the role of CBD in the cardiovascular system were inferred from small non-randomized

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studies, we aimed to conduct a randomized, triple-blind, placebo-controlled, and crossover study to examine the influence of 5-week CBD administration on blood pressure in individuals with primary hypertension (HYPER-H21–4 trial) [11]. For this trial, we used a DehydraTECH™2.0 CBD, a patented formulation that uses a performance-enhancing dehydration process to increase CBD bioavailability [11].

Apart from exploring the mere reduction in blood pressure, we also endeavored to establish putative mechanisms that may explain it. For such purpose, we took several approaches, one of which relies on the role of SNS dysfunction and the chromaffin system in primary hypertension. Specifically, we explored fluctuations of serum catestatin, a neuroendocrine peptide derived from Chromogranin A, which was shown to be implicated in blood pressure regulation and primary hypertension pathophysiology [12–14]. The primary role of catestatin is constituted in negative regulation of catecholamine spillover via neuronal nicotinic cholinergic receptor (nAChR) antagonism. Yet, studies suggest that catestatin offers many more effects, such as inhibition of beta receptors and endothelin receptors, or stimulation of histamine release via a receptor-independent mechanism [15].

Hence, in the present study, we aimed to establish how 5-week administration of CBD will affect serum catestatin concentrations, and whether reduction in blood pressure will be reflected in the change of serum concentration of this peptide.

2. Methods

2.1. Study design and population

The HYPER-H21–4 was a randomized, placebo-controlled, crossover study aimed at assessing the effects of 5-week dosing of DehydraTECH™2.0 CBD on blood pressure in patients with arterial hypertension. The detailed study protocol has been described previously [11]. The study was conducted at the Department for Integrative Physiology, University of Split School of Medicine, Split, Croatia from December 2021 to April 2022. Lexaria Bioscience Corp sponsored the trial.

For the present substudy, we selected 54 patients with Grade 1 hypertension (as defined by the contemporary European Society of Cardiology for treatment of hypertension) [16]. The study was conducted according to the guidelines in the Declaration of Helsinki. All included participants provided written informed consent prior to study enrollment, and the study protocol was approved by the Ethics Committee of University of Split School of Medicine on 15th December 2021 (Class: 003–08/21–03/0003; Reg. No.: 2181–198–03–04–21–0091). The HYPER-H21–4 trial has been registered at the ClinicalTrials.gov (NCT05346562).

2.2. Inclusion and exclusion criteria

The principal inclusion criteria were the presence of Grade 1 hypertension (140–159 mmHg of systolic and 90–99 mmHg of diastolic blood pressure), untreated or treated with ACE inhibitors, or ACE inhibitors in combination with calcium channel blockers or thiazide diuretics, age 40–70 years, body mass index (BMI) between 18.5 and 35 kg/m^2, undergoing less than 150 min of moderate-to-vigorous activity per week. Exclusion criteria included the following: smoking (including both tobacco and cannabis based products); secondary forms of hypertension; active malignant disease, any form of documented heart disease, diabetes mellitus, chronic kidney disease, gout, chronic gastrointestinal disease; significant psychiatric disorders; diagnosis or history of any seizure disorder; liver disease, confirmed on baseline blood biochemistry (described in detail in the study protocol) [11]; history of opioid use; blood pressure therapy other than stated above (e.g. ACE inhibitors with beta blockers). The above-noted inclusion/exclusion criteria were assessed using a medical screening questionnaire during a clinical examination and related baseline blood chemistry findings.

2.3. Interventions, trial visits and follow-up

Subjects were randomized in a 1:1 allocation to one of two sequences: Placebo/DehydraTECH™2.0 CBD (AB sequence) or DehydraTECH™2.0 CBD/Placebo (BA sequence).

Participants allocated in the first arm (Sequence BA: CBD (Intervention B), then Placebo (Intervention A)) received CBD in the following dosage: 225–300 mg (depending on the sex and weight of the participant) split over three times daily for the initial 2.5 weeks, and 375–450 mg split over three times for the following 2.5 weeks. Following a two-week washout, participants received CBD-matched placebo tablets for five weeks. Patients allocated in the second arm (Sequence AB: Placebo (Intervention A), then CBD (Intervention B)), received placebo for five weeks, which was followed by 5-week administration of CBD in the same regime as patients in the first arm. The study protocol outlines the DehydraTECHTM2.0 CBD capsule manufacturing process in detail [11]. Placebo capsules were filled with an organic substrate powder ingredient without any CBD substance. DehydraTECH™2.0 CBD and placebo capsules were filled into matching vegan gel capsules for blinding purposes.

Physical examination and past medical history were obtained from each patient. An altitude meter (Seca, Birmingham, UK) was used to measure height, whereas body mass was measured using Tanita DC-360 S (Tanita, Tokyo, Japan). BMI was calculated by dividing the value of body mass (kg) and the squared value of height (m^2). The waist and hip circumferences were measured at standard positions using a circumference measuring tape. The waist-to-hip ratio was calculated by dividing the measured waist and hip circumference.

Office blood pressures were measured during each visit according to guidelines for blood pressure measurement [16], using WatchBP Home A (Microlife AG Swiss Corporation, Widnau, Switzerland). Blood pressure was measured in a seating position three times during each visit, and the mean value was reported.

Blood samples for measurement of catestatin were obtained from the cubital vein using a sterile disposable needle at 4 different time points: at the start of the respective periods (CBD or Placebo) and at the end of each period. Part of the sampled blood was immediately analyzed, whereas part of the sample was aliquoted and stored at − 80 °C for subsequent analysis of biomarkers, including catestatin. All blood samples were analyzed by an experienced biochemist blinded to the allocation of a participant, using the standard operating procedures in the same certified institutional biochemical laboratory. Serum catestatin concentrations (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) were determined by ELISA. The reported sensitivity of the catestatin assay was 0.05 ng/mL, a cross-reactivity with endogenous human catestatin of 100% (intra-assay and inter-assay coefficients of variability were <10% and <15%, respectively) and with a linear range of 0.05–0.92 ng/mL.

2.4. Statistical analysis

The data was analyzed using statistical software SPSS statistics (version 29.0, IBM, Chicago, IL, USA) and Prism 6 for Windows® (version 9.4.1, GraphPad, La Jolla, CA, USA). Quantitative data were expressed as mean ± SD, mean ± SEM and 95% CI, or median and interquartile range, as deemed appropriate. On the other hand, qualitative data was expressed as a whole number and percentage (n (%)). Kolmogorov-Smirnov test was used to assess the normality of data distribution. A comparison of quantitative variables was conducted using Student's t-test and Mann-Whitney U test, depending on normality of data distribution, while qualitative data was compared using chi-squared test. To explore the dynamic in serum catestatin concentrations after each period, Friedman test with post hoc Conover test was employed. Fluctuations in MAP were assessed using repeated measure

ANOVA. We introduced variable Δ_{CBD}Catestatin, which was defined as the difference between serum catestatin concentration at the end of CBD dosing period and catestatin concentration at the start of the CBD dosing period. Accordingly, we also introduced Δ_{CBD}MAP, a variable that was defined as the difference between MAP at the end of CBD dosing and MAP at the start of the CBD dosing period. To examine correlation between serum catestatin concentration and MAP in each respective time point, and correlation between catestatin, Δ_{CBD}Catestatin and Δ_{CBD}MAP, we employed Spearman's rank-order correlation analysis. The r correlation coefficient (rho) and two-tailed significance (p) values were reported in this analysis. The significance was set at $p < 0.05$ for all comparisons.

3. Results

In the present analysis, 54 patients with a primary form of hypertension were included. The analysis enrolled 33 male subjects and 21 female subjects. The average age of participant was 55.3 ± 7.0 years, whereas average blood pressure was 103.2 ± 10.0 mmHg. The baseline characteristics of interest were outlined in detail in Table 1.

5-week administration of DehydraTECH™2.0 CBD formulation reduced serum catestatin concentration in comparison to baseline (13.50 [10.85–19.05] vs. 9.65 [6.37–12.26] ng/mL, $p < 0.001$) (Fig. 1). On the other hand, during the placebo period, such dynamic was not observed (16.11 [10.82–19.78] vs. 14.31 [10.07–19.90] ng/mL, $p = 0.928$) (Fig. 1). Accordingly, MAP dropped by 4.26 ± 1.26 mmHg following the 5-week period of CBD dosage, but not during Placebo period (Fig. 2). Change in serum catestatin concentration and MAP reduction did not depend on the sequence of CBD dosing (A then B vs B then A).

Furthermore, serum catestatin concentrations correlated with MAP at the start of each period (r = 0.334, $p = 0.015$ for Placebo period, and r = 0.337, $p = 0.014$ for CBD period) (Fig. 3).

Moreover, serum catestatin levels at the start of the treatment period demonstrated negative correlation with change in Δ_{CBD}MAP, defined as the difference between MAP at the end of 5-wk CBD administration and baseline MAP (r = −0.474, $p < 0.001$) (Fig. 4).

In line with this, multiple linear regression analysis established that Δ_{CBD}MAP correlates with baseline catestatin irrespective of age, BMI and treatment status (previous antihypertensive treatment) (β ± SE, −0.52 ± 0.13, $p < 0.001$). Finally, Δ_{CBD}Catestatin, defined as the difference between serum catestatin concentration at the end of 5-wk CBD administration and baseline catestatin, showed a strong positive correlation with Δ_{CBD}MAP (r = 0.712, $p < 0.001$) (Fig. 5).

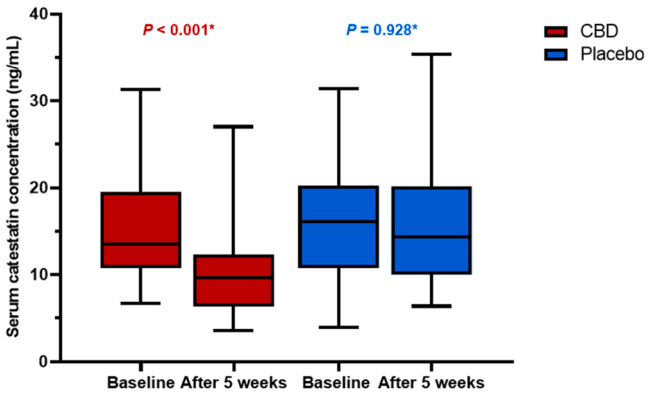

Fig. 1. Effect of 5-week CBD administration on serum catestatin levels. Data is presented as median and IQR. *Friedman test with post-hoc Wilcoxon test.

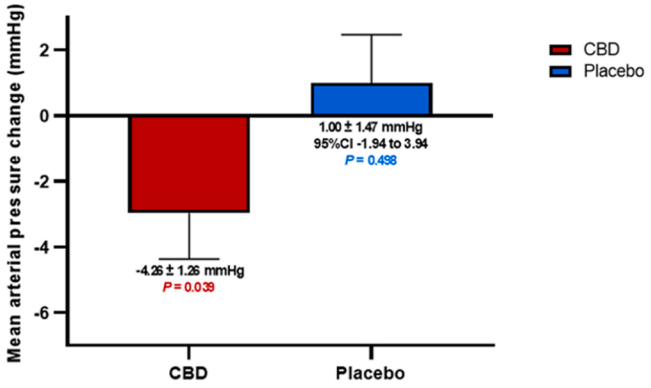

Fig. 2. Effect of 5-week CBD administration on office mean arterial pressure. Data is presented as mean ± SEM and 95% Confidence Interval. Data were analyzed via repeated measure ANOVA.

Table 1
Baseline characteristics of patients.

Parameters	Total (n = 54)
Age, years	55.3 ± 7.0
Male sex, n (%)	33 (61.1%)
Family history of CV disease, n (%)	24 (44.4%)
Time since AH diagnosis, years	4 (2–6)
Body mass index, kg/m^2	28.5 ± 3.4
Waist-to-hip ratio	0.95 ± 0.08
Total cholesterol, mmol/L	5.6 ± 1.0
LDL-C, mmol/L	3.4 ± 0.9
HDL-C, mmol/L	1.5 ± 0.4
Triglycerides, mmol/L	1.6 ± 0.9
Aspartate transaminase, U/L	25.4 ± 9.2
Alanine transaminase, U/L	27.5 ± 14.8
Gamma-glutamyl transferase, U/L	18 (13–28)
Creatinine, μmol/L	76.2 ± 14.9
Bilirubin, μmol/L	9.1 ± 3.8
HbA1c, %	5.7 ± 0.4
Therapy	
ACEi	14 (48.3%)
ACEi + CCB	11 (37.9%)
ACEi + thiazide diuretic	4 (13.8%)
No therapy	25 (46.3%)
Office BP at baseline	
SBP, mmHg	133.4 ± 12.5
DBP, mmHg	83.0 ± 10.9
MAP, mmHg	103.2 ± 10.0

Data presented as mean ± SD, n (%) or median (IQR). Abbreviations: AH: arterial hypertension; ACEi: angiotensin-converting enzyme inhibitors; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CCB, calcium channel blockers; CV: cardiovascular; BP: blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

4. Discussion

To the best of our knowledge, this is the first time that the association between catestatin and the hemodynamic effects of CBD supplementation has been explored. Available evidence implies that CBD, and other constituents of cannabis as well, may produce significant hemodynamic effects [8,10]. For instance, early reports associated cannabinoids with orthostatic hypotension [17]. Subsequently, multiple studies explored how CBD affects blood pressure and vascular tone, with somewhat conflicting results. Preclinical data (mice, piglets, rats), as summarized in a meta-analysis by Sultan et al., implies that administration of CBD has no effect on blood pressure or heart rate under control conditions but reduces both of these in stressful conditions, while increasing cerebral blood flow [18]. Among human studies, a small-scale randomized clinical trial performed on healthy volunteers [19], showed that CBD significantly reduced resting MAP after acute dosing, but did not affect ambulatory blood pressure values after six days of repeated dosing. The same study showed that CBD reduced arterial stiffness and improved

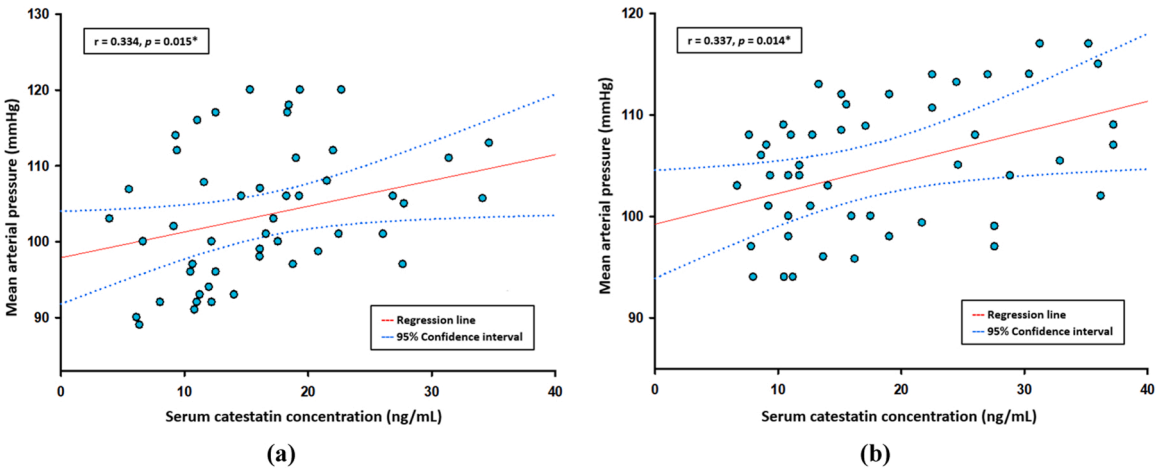

Fig. 3. Correlation between serum catestatin concentrations and mean arterial pressure. a) at the start of Placebo period; b) at the start of CBD period. Abbreviations: r: correlation coefficient; CBD: cannabidiol *Spearman rank correlation analysis.

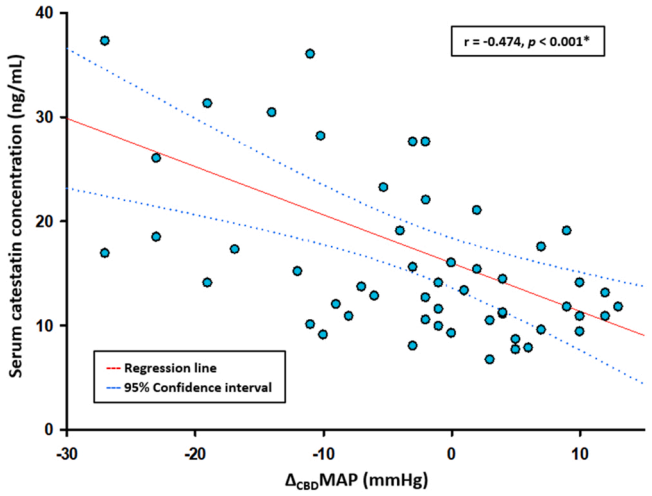

Fig. 4. Correlation between serum catestatin concentrations at the start of CBD period and Δ_{CBD}MAP. Abbreviations: r: correlation coefficient; MAP: mean arterial pressure; CBD: cannabidiol *Spearman rank correlation analysis.

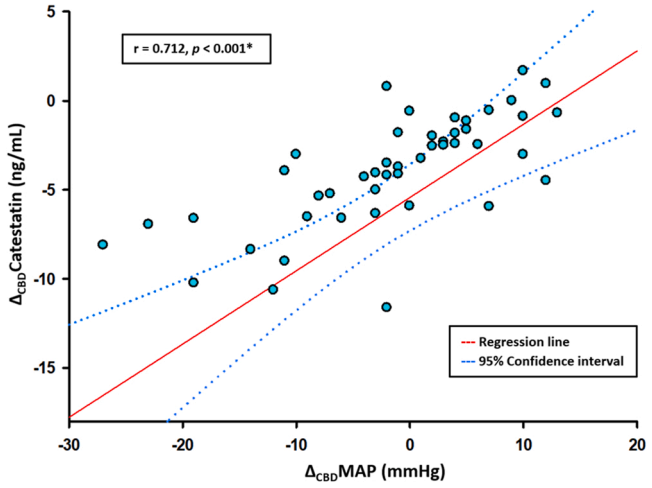

Fig. 5. Correlation between Δ_{CBD}Catestatin and Δ_{CBD}MAP. Abbreviations: r: correlation coefficient; MAP: mean arterial pressure; CBD: cannabidiol *Spearman rank correlation analysis.

flow-mediated dilation after 7 days of repeated administration. On the other hand, a randomized crossover study showed that CBD reduced systolic blood pressure in response to exercise stress after both acute and repeated dosing. In contrast, a separate study [20] showed that patients treated with CBD had lower systolic but not diastolic blood pressure in response to cold pressor test. Finally, we previously demonstrated that oral CBD did not affect blood pressure, yet, attenuation of MAP was observed when CBD was administered under a similar formulation and dose as in the current study [21].

Importantly, the hemodynamic effects of CBD are not a result of its agonistic effect on CB1 and CB2, as CBD has low affinity for these receptors [10,22]. Conversely, CBD is can antagonize the actions of CB1/CB2 receptor agonists at concentrations lower than those required to evoke the response on CB1/CB2 (nanomolar vs. micromolar concentrations) [23,24]. Additional pathways that may explain CBD hemodynamic effects include an increase in endogenous cannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well as other biologically active compounds, such as serotonin, dopamine or adenosine [8,25,26]. It is worth mentioning that CBD may also trigger a response from CB1 and CB2 receptors indirectly via inhibition of uptake and breakdown of endogenous cannabinoids AEA and 2-AG [27]. This mechanism may be particularly important for CBD effect in hypertension, as this condition has been associated with changes in the endocannabinoid system (increase in AEA) [28,29]. Of note, CBD has also been shown to cause endothelium-dependent vasodilation on an in vitro model of human arteries [30,31]. On a separate note, cannabinoids were shown to modulate SNS activity by multiple pathways. Firstly, preclinical data suggests that cannabinoids may modulate α2-adrenoreceptor function, thus altering the SNS response [32]. On the other hand, CB1 receptors located on presynaptic nerve terminals have the ability to modulate the release of neurotransmitters from corresponding neurons in a heteroreceptor-typical way [33], thus increasing or decreasing neuronal excitability depending on neurotransmitters and region affected. Furthermore, it has been shown that CB1 are abundant on peripheral sympathetic nerve terminals, where they modulate adrenergic signaling. It is worth noting in this regard that CB1 receptors express features of functional antagonism. Namely, the administration of exogenous cannabinoids and/or elevation of endogenous levels of the full CB1 agonist, can both lead to downregulation of CB1 [34]. Unfortunately, the complexity of the interaction between CBD, endocannabinoids, and cannabinoid receptors impedes us from reaching exact conclusions about mechanisms by which CBD supplementation alters SNS activity.

Catestatin, a potent physiological inhibitor of catecholamine spillover, may be a missing link that could explain the above-noted

interaction at least to some extent [15]. Specifically, we demonstrated that serum catestatin levels reduce after five weeks of CBD supplementation, but not after placebo. We hypothesize that such reduction reflects the reduced need for sympathoinhibition. This is in line with the results of our previous study [12] in which we showed that patients with untreated hypertension had higher catestatin concentrations compared to thosepatients treated with antihypertensives. Moreover, accumulating data suggests that catestatin represents a compensatory mechanism aiming at blood pressure reduction. For instance, catestatin decreases blood pressure in an acute setting by direct vasodilation and by mediating central nicotinic acetylcholine receptors and β-adrenoceptors, whereas *ChgA*-gene knockout was shown to cause an increase in blood pressure that is normalized by intraperitoneal administration of catestatin [35–38]. Independent correlation between catestatin at the start of the treatment period and the extent of change in MAP (Δ_{CBD}MAP) upon CBD treatment, suggests that higher levels of catestatin herald more significant reduction in blood pressure. We may hypothesize that this finding is not a result of CBD solely but rather of the drop in blood pressure itself and can therefore represent an interesting concept for future studies on antihypertensive medications, as biomarkers of response to antihypertensive treatment are virtually inexistent. This hypothesis is further supported by the strong correlation observed between the extent of change in MAP and concomitant change in serum catestatin levels after five weeks of CBD supplementation. The fact that serum catestatin concentrations correlate with office values of MAP is in line with our previous study conducted on patients with hypertension and healthy individuals.

The present study bears several limitations. Firstly, the study was conducted in a single center and included Caucasian population exclusively. Secondly, only patients with mild hypertension were included, therefore limiting the applicability of results on patients with more severe forms of hypertension. Finally, as only DehydraTECH™2.0 CBD formulation was used in the present study, whether the observed effects are applicable to other CBD formulations remains elusive.

5. Conclusions

In conclusion, the substudy of the HYPER-H21–4 trial implies that reduction in blood pressure after CBD treatment is accompanied by a concomitant reduction in serum catestatin levels. Moreover, the extent of blood pressure reduction seems to be heralded by baseline catestatin concentration, implying that baseline values of catestatin may predict the antihypertensive response to CBD. Finally, as serum catestatin concentrations correlated with MAP at each time point, except at the end of CBD period, catestatin and CBD are likely interconnected by mechanisms beyond the blood pressure regulation. Overall, the results of the present study imply that antihypertensive effects of CBD may be explained by its interaction with the sympatho-chromaffin system, although further research is warranted.

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CRediT authorship contribution statement

Marko Kumric: Conceptualization, Methodology, Investigation, formal analysis, Writing – original draft preparation. **Goran Dujic:** Visualization, Investigation, Formal analysis, Writing – original draft preparation. **Karla Svagusa:** Visualization, Investigation, Formal analysis Writing – review & editing. **Josip Vrdoljak:** Visualization, Investigation, Formal analysis, Writng – original draft preparation. **Tina Ticinovic Kurir:** Visualization, Investigation, Formal analysis, Writing – original draft preparation. **Daniela Supe-Domic:** Visualization, Investigation, Formal analysis, Writing – original draft preparation. **Zeljko Dujic:** Conceptualization, Funding acquisition, Resources, Project administration, Writng– review & editing. **Josko Bozic:** Conceptualization, Funding acquisition, Resources, Project administration Writing – review & editing.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Data Availability

Data will be made available on request.

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