Effects of a CBD-containing Supercritical Fluid Extract of Hemp on Markers of Optimal Wellness, Stress Resilience, and Recovery in Healthy Subjects

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ABSTRACT

The purpose of this placebo-controlled, double-blind study was to determine the effects of a commercially available (i.e. dietary supplement) Hemp Oil Extract product on various markers of physical and mental stress resilience, and perceived recovery from normal daily physical & mental stress. Secondary purposes were to collect information on perceived appetite, mood, feelings of well-being, sleep quality, body composition and safety information via standard clinical chemistry panels of sera and plasma.

Methods: Using a randomized, placebo-controlled, double-blind design, 65 overweight, but otherwise healthy men (n = 32) and women (n = 33) (mean ± SD age, BMI: 35.2 ± 11.4 yr, 28.5 ± 3.3 kg/m2) ingested either Hemp Oil Extract [HEMP, 60 mg/d PlusCBD Oil™ (15 mg hemp-derived CBD)] or a placebo (PLA) every day for six weeks. Subjects followed their normal diet and a routine of low intensity physical activity (30 min of walking exercise 5 days per week). Outcome variables included changes in stress resilience, a 14-item panel of various psychometric parameters, heart-rate variability (LF, HF, LF/HF ratio, rMSSD), plasma chromogranin A, body composition (lean mass, fat mass, bone mineral content, VAT fat via DEXA) as well as general markers of health (heart rate, blood pressure, and comprehensive clinical chemistry panels of serum and plasma) before and after six weeks of supplementation. Data were analyzed via ANOVA, t-tests ($p \leq 0.05$) and effect sizes (ES).

Results: Preliminary analyses revealed significant decreases in appetite (-6.2%, p=0.04, ES=0.22) and improvements in sleep quality (+22.0%, p=0.009, ES=0.54), sleep quantity (+21.3%, p=0.02, ES=0.58) and pleasure from life (+12.5%, p=0.006, ES=0.46) in HEMP only. All values for hepato-renal function (AST, ALT, BUN, creatinine, total bilirubin, alkaline phosphatase), cardiovascular health (heart rate, blood pressure), fasting blood lipids (cholesterol, triglycerides, HDL, LDL) whole blood cell counts (hemoglobin, hematocrit, RBC, MCV, MCH, MCHC, RDW, differential white cell counts) remained within normal clinical limits, and no between-group differences over time were noted.

Conclusions: Collectively, these seminal findings in healthy subjects indicate that six weeks of HEMP PlusCBD Oil™ supplementation can improve measures of sleep homeostasis, reduce appetite, and enhance quality of life. Ongoing and future analyses will examine changes in stress resilience, autonomic nervous system function, body composition, inflammatory cytokines, adipokines, as well as targeted gene expression/transcriptome (NFkB, NLRP3, UCP, PGC1a), etc.

BACKGROUND

The endocannabinoid system (ECS) is a master endogenous homeostatic system consisting of 1) lipid based signaling compounds (endocannabinoid ligands), 2) specialized cannabinoid receptors found throughout most tissues in the body and 3) biosynthetic and catabolic enzymes that regulate the endogenous ligands. Through both direct and indirect actions, endocannabinoids modulate and influence a variety of physiological systems, including pain, inflammation, thermoregulation, appetite, energy balance, muscle control/coordination, sleep health, stress responses, motivation, mood, and memory. There is a wide variety of *Cannabis sativa* L. cultivars with a complex phytochemical profile containing terpenophenolic cannabinoids and 400+ constituents that are distinguished by their chemical and genetic profile. Hemp is generally characterized as a cultivar of *C. sativa* whose predominant cannabinoid is cannabidiol (CBD), with a relatively low level of delta-9 tetrahydrocannabinol (THC) when assayed on a dry weight basis. Herein, we report on the psychometric indices of sleep, appetite, quality of life, and biomarkers of safety from supplementation with a CBD containing supercritical CO2 extract of the aerial parts of hemp.

MATERIALS & METHODS

This was a prospective, randomized, double-blind, parallel-groups clinical trial in 65 apparently healthy men and women. Subjects were matched according to gender (sex) and BMI prior to being randomly assigned to receive, in a double-blinded manner, either Hemp Oil Extract soft gel product or a Placebo soft gel. Subjects randomized to the active product (i.e. hemp soft gel) group consumed 1 softgel daily in the morning every day for six weeks. Subjects randomized into the placebo group consumed an olive oil softgel of equivalent size and appearance. Supplements were prepared and packaged in coded generic containers for double-blind administration.

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MATERIALS & METHODS

INCLUSION CRITERIA:

- Subjects provided written and dated informed consent to participate in an IRB approved study.
- Subjects were in good health as determined by medical history and routine blood chemistries.
- Subjects were male or female between the ages of 18 and 55 (inclusive).
- Female subjects must agree to use barrier contraceptive methods during sexual intercourse for the duration of the study. All females underwent pregnancy testing (urine HCG screen) before being screened and at each visit unless they presented evidence of surgical sterilization by tubal ligation, bilateral oophorectomy or hysterectomy.
- Subjects had a Body Mass Index of 25-35 (inclusive).
- Subjects were willing and able to comply with the daily activity and supplement protocol.
- Subject were willing and able to comply with the visit schedule.
- Subjects were normotensive (resting systolic blood pressure ≤140 mm Hg and diastolic blood pressure ≤ 90 mm Hg), have a normal resting heart rate (≤90 per minute).

EXCLUSION CRITERIA:

- Subjects that exercised more than three times per week.
- Subject had used weight loss medications within the past three months of Screening visit.
- Subject was on thyroid medication at a dose that is not considered stable. Stable is defined as using the same dose consistently for at least 90 days.
- Subjects with any metabolic disorder including known electrolyte abnormalities, diabetes (or fasting glucose ≥126 mg/dL at the screening visit), unstable or unmanaged thyroid disease, or hypogonadism.
- Subjects with a history of hepato-renal, musculoskeletal, autoimmune, neurologic disease, or any other medical condition deemed exclusionary by the medical staff.
- Subjects taking anti-anxiety, anti-depressant, psychotropic hyperlipidemic, hypoglycemic, anti-coagulant or androgenic medications; nitrates/nitrate derivatives, and PDE-5 inhibitors; and other vasodilatory agents such as calcium channel blockers and beta blockers.
- Subject with an active gastrointestinal disorder such as peptic ulcer disease or malabsorption syndrome (mild lactose intolerance or gastroesophageal reflux diseases are acceptable).
- Subjects who had taken anabolic steroids, growth hormone, IGF-1 or other anabolic drugs within the past year.
- Subjects who were pregnant, trying to become pregnant, or who were nursing.
- Subjects who had taken any nutritional supplements that may affect sleep, mood or healthy stress response (including but not limited to Ashwagandha, Valerian root, Melatonin, L-theanine, 5-HTP), or that may affect anabolic/catabolic hormone levels (e.g., androstenedione, DHEA, etc.) within four weeks prior to the start of the study.
- Subjects with history of heart disease, peripheral vascular disorders or vaso-occlusive or vasospastic syndromes, psychiatric disorders, or history of malignancy in the previous 5 years except for non-melanoma skin cancer (basal cell cancer or squamous cell cancer of the skin.
- Subject had a recent history of (within 3 months of Screening Visit) or strong potential for alcohol or substance abuse. Alcohol abuse defined as >14 drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1½ oz distilled spirits).
- Subject had been hospitalized within the past one-year for any mental or emotional illness.
- Subjects who had any known allergy to any of the ingredients in any of the test products.
- Subjects who were participating in other research studies.
- Individual had a condition the Investigator believed would interfere with his or her ability to provide informed consent, comply with the study protocol, or which might confound the interpretation of the study results or put the person at undue risk.
- Subjects who smoked or used any tobacco or nicotine containing products within the past year.
- Subjects with syndromes or prescribed medications that may influence body composition or CVD (e.g. prednisone, Ritalin, Adderall, GH); also protease inhibitors/antivirals (nucleic acid analogs).

DIET:

- All subjects remained on their standard (pre-study) diet. The research staff met with each subject to explain the proper procedures for recording dietary intake and maintaining their standard baseline diet.
- Each subject's baseline diet (3 days: two weekdays & one weekend day) was analyzed via NutriBase IX (Clinical Edition) to determine its energy and macronutrient content.
- Additional 3-day diet records were analyzed prior to the last day of testing (i.e. during week 6) to verify that eating habits remained consistent throughout the study.
- Subjects were asked to provide a log and duplicate their 24-hour diet prior to screening, week 0 and week 6.

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EXERCISE AND PHYSICAL ACTIVITY:

- Subjects were asked to increase their habitual physical activity to 30 minutes of walking exercise at least 5 days per week. To monitor compliance to the exercise regimen, each subject documented their walking exercise in a training log that was brought with them at each visit.
- Each subject's physical activity was assessed via a standardized questionnaire at baseline and again on the last day of testing (at pre and post visits).

SUPPLEMENTATION:

- After qualifying for the study, subjects were matched according to gender (sex) and BMI prior to being randomly assigned to receive, in a double-blinded manner, either Hemp Oil Extract soft gel product or the Placebo soft gel.
- Subjects randomized to the active product (i.e. hemp soft gel) group consumed the manufacturers recommended dose (i.e. 1 softgel daily in the morning) every day for six weeks. Subjects randomized into the placebo group consumed an olive oil softgel of equivalent size and appearance.
- Supplements were prepared and packaged in coded generic containers for double-blind administration.
- Compliance to the supplementation regimen was monitored by daily logs.

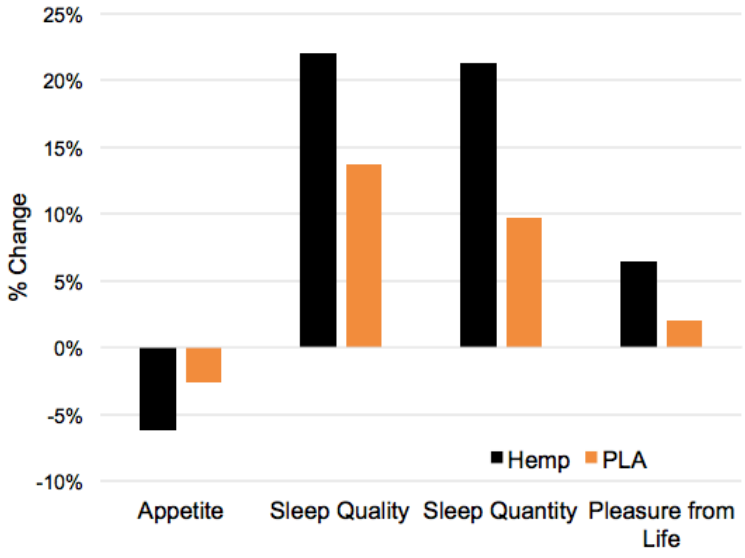
STATISTICAL ANALYSES:

- Preliminary between-group analyses included two-way ANOVA, while within-group changes from baseline were assessed via ANOVA (for comparing 3 means) and t-tests (for 2 means). Significance was set *a priori* at $P \leq 0.05$ and trends were defined as $0.051 \leq P \leq 0.10$.
- Planned (future) analyses will include cluster analysis, ANCOVA, and regression.

RESULTS

				95% CI (Delta)	
Variable		**Week 0**	**Week 6**	**Lower**	**Upper**
Hemoglobin (g/dl)	HEMP	14.3 ± 1.2	14.1 ± 1.3	-0.29	0.30
	PLA	14.4 ± 1.1	14.3 ± 1.3		
Hematocrit (%)	HEMP	42.1 ± 3.1	42.0 ± 3.2	-0.88	0.91
	PLA	42.4 ± 2.9	42.3 ± 3.3		
Glucose (mg/dl)	HEMP	85.9 ± 10.0	87.2 ± 9.9	-3.03	6.96
	PLA	88.2 ± 7.8	87.5 ± 7.3		
Blood Urea Nitrogen (g/dl)	HEMP	14.2 ± 3.6	13.5 ± 4.7	-2.24	1.09
	PLA	14.2 ± 4.3	14.2 ± 4.8		
Creatinine (g/dl)	HEMP	0.92 ± 0.16	0.92 ± 0.19	-0.03	0.06
	PLA	0.89 ± 0.18	0.88 ± 0.19		
Bilirubin (g/dl)	HEMP	0.50 ± 0.33	0.51 ± 0.31	-0.01	0.22
	PLA	0.57 ± 0.34	0.48 ± 0.29		
Alkaline Phosphatase (U/L)	HEMP	60.6 ± 14.8	63.0 ± 14.8	-2.63	4.98
	PLA	66.3 ± 15.1	67.6 ± 19.3		
AST (U/L)	HEMP	25.2 ± 8.8	23.5 ± 6.1	-8.10	-0.18
	PLA	22.7 ± 8.8	25.2 ± 10.2		
ALT (U/L)	HEMP	23.6 ± 14.3	21.2 ± 9.8	-9.43	0.52
	PLA	22.7 ± 12.7	24.8 ± 16.7		
Total Cholesterol (mg/dl)	HEMP	176.4 ± 33.1	181.9 ± 28.9	-1.65	20.18
	PLA	184.3 ± 29.7	180.5 ± 35.1		
Triglycerides (mg/dl)	HEMP	89.3 ± 52.8	89.8 ± 58.2	-26.23	24.89
	PLA	92.2 ± 63.5	93.4 ± 64.3		
HDL Cholesterol (mg/dl)	HEMP	54.0 ± 12.3	57.5 ± 13.3	1.66	8.25
	PLA	60.3 ± 18.0	58.7 ± 17.5		
LDL Cholesterol (mg/dl)	HEMP	104.5 ± 27.3	106.5 ± 26.8	-5.23	12.98
	PLA	105.6 ± 30.3	103.7 ± 31.3		

Values are mean +/SD and 95% confidence intervals. There were no GxT interactions.



Percent change from baseline (relative to week 6). All variables displayed observed statistically significant changes in the HEMP group only. See abstract for p-values.

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CONCLUSIONS

- These data represent the first report we are aware of regarding the safety and efficacy of a commercially available finished product (PlusCBD Oil™) containing a hemp-derived, CBD-rich extract in healthy humans.
- HEMP (PlusCBD Oil™) supplementation at 15mg active CBD containing a broad array of minor phytocannabinoids, terpenes, tocopherols/tocotrienols, and fatty acids can improve self-reported psychometric measures of sleep, quality of life (life satisfaction) and reduce appetite, while demonstrating no adverse effects on standard biomarkers of safety.
- Future studies are warranted to fully characterize the complex phytochemical composition of the commercial HEMP extract (PlusCBD Oil™) finished product.
- Ongoing and future analyses will interrogate effects on inflammatory cytokines, HPA axis/stress hormones and targeted gene expression profiles, along with assessing PK with ascending doses to assess bioavailability, metabolism and elimination half-life of HEMP extract delivered as part of a complex spectrum of phytochemical constituents.

REFERENCES AND DISCLOSURE

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