Weight Loss and Therapeutic Metabolic Effects of Tetrahydrocannabivarin (THCV)-Infused Mucoadhesive Strips

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ABSTRACT

Objective: Metabolic syndrome is due to dysregulation that starts with fat accumulation, causing inflammatory response, insulin resistance, dyslipidemia, hypertension, and fatty liver disease. The endocannabinoid system, via cannabinoid receptor type 1 (CB_1), has been shown to be involved with energy homeostasis and regulation of appetitive behavior via activity in the hypothalamus, limbic forebrain and amygdala and in the peripheral tissues including adipose, liver and muscle. Therefore, two phytocannabinoids, tetrahydrocannabivarin (THCV), a CB1 neutral antagonist, and cannabidiol (CBD), a negative allosteric modulator of CB1, are expected to have therapeutic metabolic benefits, including weight loss. **Method:** A placebo-controlled study was conducted on 44 subjects (31 females and 13 males) with an average age of 51.75. The study evaluated the efficacy of two different doses of THCV and CBD (8 mg THCV/10 mg CBD in the lower dose and 16 mg THCV/20 mg CBD in the higher dose), taken once daily for 90 days via mucoadhesive oral strips, for weight loss and improvement of certain metabolic markers. **Results:** Use of the THCV/CBD strip was associated with statistically significant weight loss, decreases in abdominal girth, systolic blood pressure, and total and LDL cholesterol. The study was limited by small sample sizes in both the high dose and placebo groups. **Conclusions:** The 16 mg/20 mg daily dose was superior for weight loss compared to the 8 mg/10 mg daily dose; both sets of results differed from placebo in a way that was statistically significant. The results of this study were congruent with the prior unpublished studies of a hemp extract containing significant percentages of THCV, CBDV and CBD.

Key words: = THCV; weight loss; metabolism; metabolic syndrome; hypercholesterolemia

Metabolic Syndrome

According to the National Institutes of Health (NIH), Metabolic syndrome is a group of conditions that occur together due to the same underlying metabolic changes. Metabolic syndrome follows a gradual progression from truncal adiposity, obesity, elevated blood pressure, glucose intolerance, dyslipidemia to diabetes mellitus and fatty liver disease. According to the National Cholesterol Education Program (NCEP) definition, metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL). Metabolic syndrome has become epidemic in societies with Western diets (Swarup et al., 2022). Over 1.9 billion adults worldwide are overweight or obese, and almost half of these adults will have metabolic syndrome (Pekgor et al., 2019).

Current evidence supports chronic low-grade inflammation from fat deposits as the origin of adverse metabolic effects. This happens when adipose tissue releases proinflammatory cytokines, resulting in localized insulin resistance

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(Swarup et al., 2022). Genetic and epigenetic factors, excess calories, and lack of physical activity are major contributors to the condition (Fathi Dizaji, 2018). High caloric intake resulting in excess visceral fat storage activates most of the pathways of metabolic syndrome (Fujita et al., 2006).

The Endocannabinoid System and Appetite Regulation

The endocannabinoid system, via the cannabinoid receptor type 1 (CB_1), has been shown to be involved with energy homeostasis and regulation of appetitive behavior in the brain, including the hypothalamus, limbic forebrain and amygdala, and in the peripheral tissues, including adipose, liver and muscle tissue (Cristino, Becker, & Di Marzo, 2014).

It is thought that as humans evolved, the endocannabinoid system developed a regulatory pathway to encourage food-seeking behavior in times of food scarcity; however, since the advent of modern agriculture and increased availability of high-calorie, low-nutrient foods, we have seen an exponential rise in obesity, especially in the West. It stands to reason that decreasing endocannabinoid activity would be an effective treatment for obesity and its metabolic consequences (Kunos & Osei-Hyiaman, 2008).

Tetrahydrocannabivarin (THCV) and Cannabidiol (CBD)

Tetrahydrocannabivarin (THCV), a naturally occurring, non-psychoactive minor phytocannabinoid, is only present in tiny amounts in most *cannabis sativa* strains; recently, however, the biosynthesis of hemp-derived cannabidiol (CBD) has made THCV available in commercially viable quantities. Being a full neutral CB_1 antagonist and a partial CB_2 antagonist, THCV is unique in its effects (Thomas et al., 2005). Although concerns have been raised that taking THCV would result in a false positive urine test for tetrahydrocannabinol (THC), this concern was noted and factored into the study design (Englund et al., 2016).

Fasted and non-fasted mouse studies have shown decreased food intake and body weight, and increased energy expenditure, glucose tolerance, and insulin sensitivity in response to THCV (Wargent et al., 2013). A similar human study suggested that THCV modulated food intake by decreasing connectivity between the amygdala and the precuneus appetite and reward centers of the brain (Tuulari et al., 2015).

CBD is a negative allosteric modulator of the CB_1 receptor and a partial CB_1 antagonist, compared to THCV, which is a full neutral CB_1 antagonist (McPartland et al., 2015). In addition, CBD has well-documented anti-inflammatory effects, which are systemically likely to be therapeutic for the low-grade inflammation underlying the pathophysiology of the Metabolic syndrome (Jadoon et al., 2016). Because these effects of CBD work through different mechanisms, CBD may facilitate the appetite and metabolic effects seen with THCV (Pertwee, 2008).

Previous animal studies have shown that THCV acts by neutrally blocking the CB_1 receptor in the hypothalamus and the gut (pancreas, liver and intestinal tract; Abioye et al., 2020). The CB_1 blockade switches the body into the 'fasting' state, so the body defaults to burning abdominal fat (Sidibeh et al., 2017).

An increasing body of unpublished clinical research has shown that small daily doses of Hempson Oil ® (hemp-extract high in CBD, THCV and cannabidivarin, CBDV) taken orally have consistent effects of weight loss, reduction in abdominal girth, blood sugar (HgbA1c), and blood lipid ratios.

The current study will evaluate the efficacy of using THCV and CBD isolates infused into mucoadhesive oral strips for therapeutic effects on weight loss, abdominal girth, and improvement of certain metabolic markers.

THCV and Positive THC Drug Test

A review of existing scientific literature failed to identify any study of humans using THCV showing a positive urine test for THC metabolites. However, because the possibility remains that some metabolites excreted in the urine may cause a false-positive result on a drug test, a subgroup of subjects using THCV were submitted to urine THC screening following the study.

METHODS

This study was designed to focus on otherwise healthy obese adults in the early stages of

developing metabolic syndrome. The focus was on reducing adiposity, the underlying pathophysiologic feature of the metabolic syndrome. Fifty-six adults were recruited via social media ad campaigns. Selection criteria were for subjects who met the clinical definition of obesity (BMI ≥ 30) without comorbid diabetes or cardiovascular disease. Subjects with normal or less than Stage II hypertension (systolic BP greater than or equal to 160 mm Hg and/or diastolic BP less than 100 mm Hg) who were under a physician's supervision were included; subjects with active cardiovascular or respiratory symptoms were excluded.

Subjects were enrolled via correspondence with an administrative assistant not otherwise involved in the study. Subjects additionally underwent an entrance examination by a blinded independent physician to screen for diabetes, active cardiovascular or pulmonary disease, or other confounding health conditions prior to starting the study. All were determined to be clinically stable.

Two doses were used for the intervention. These were 8 mg of THCV with 10 mg of CBD and 16 mg of THCV with 20 mg of CBD once daily. The THCV doses were chosen based on the known pharmacokinetics (PK) and pharmacodynamics (PD) of the structurally similar tetrahydrocannabinol (THC) molecule, an unpublished clinical trial using THCV and CBD for the treatment of type II diabetes, and five unpublished studies of Hempson® oil, a hemp-derived oil with 17% THCV and 50% CBD. The addition of CBD was limited to very small doses, based on the small load bearing of the mucoadhesive strip.

All primary outcome measures (defined as changes in weight and abdominal girth) and secondary outcome measures (defined as changes in systolic and diastolic blood pressure and changes in fasting blood work lipid profile, blood sugar, HgbA1c, liver and kidney function studies) were determined at the beginning of the study (day 0) and at the end of the study (day 90).

LabCorp offices in the greater Tampa area were used for all lab collection and analysis. The same lab assay and methodology were used for the repeat comparative testing. The specific assays used by LabCorp were not reviewed.

Initial and final biometric measurements taken included blood pressure, blood oxygen, temperature, height, weight, and abdominal girth. For people with active periods, the ending biometrics were to be taken during the same phase of their menstrual cycle as when they had their initial measurement taken - around 90 days later.

Abdominal girth was obtained using the NIH-recommended procedure, in which a horizontal line is marked slightly above the outer edge of the right iliac crest, and it intersects with a vertical line along the midaxillary line; the measuring tape is then positioned horizontally around the abdomen at the same level as this marked point on the right side of the trunk.

A random number generator program was used to assign subjects to one of three groups through simple randomization: Group A (single dose group), Group B (double dose group,) and Group P (placebo/control group). The trial design was a parallel-group randomized trial, with unequal allocation ratio of 2:1:1 (Group A, Group B, Placebo). Allocation was double-blind to both the subject and the investigator. Subjects, care providers, and the lead investigator were blinded to the entire group allocation process.

Subjects were provided with a 90-day supply of their respective dose (based on group assignment) and were instructed to take the dose once daily by mouth on an empty stomach in the morning, with no additional changes to their diet or exercise routines. Subjects agreed to refrain from the use of cannabis, CBD, or other hemp products throughout the duration of the study.

Text message reminders were sent daily between 8 and 9 AM to each subject to a prior approved personal cell phone number, advising them to take their dose, confirm once it had been taken, and report on any adverse effects. The text messaging was HIPAA compliant. Each subject was paid $100 upon completion of initial lab testing and another $100 after completing a 90-day exit interview and final lab testing.

After passing the inclusion criteria, the subjects gave their written informed consent to the independent physician using the World Health Organization – Research Ethics Review Committee (WHO ERC) template for clinical trials. The hemp-based extract was considered minimal to very low risk based on prior research. A data safety monitoring plan (DSMP) was implemented and approved by the Institutional Review Board (IRB) to ensure appropriate

oversight and monitoring of the clinical investigation. Subject monitoring was implemented through the daily text responses, as well as before and after physical examinations and before and after laboratory studies. Subject privacy, data integrity, product accountability, coordination, and documentation were ensured throughout the study. Follow-up on subjects 'lost to follow-up' was conducted.

A total of 44 subjects across three groups completed the full course of the 90-day study. Twenty-four subjects took one proprietary mucoadhesive strip infused with L-arginine and menthol daily, containing 8 mg of THCV and 10 mg of CBD (Group A); 10 subjects took two proprietary mucoadhesive strips infused with L-arginine and menthol daily, containing a total of 16 mg of THCV and 20 mg of CBD (Group B); and 10 subjects took one proprietary mucoadhesive strip infused with L-arginine and menthol as the placebo daily (Group P). Each mucoadhesive strip came in a factory-sealed aluminum foil envelope marked with a code to denote the contents to the investigators.

A total of 8 subjects across the three groups did not complete the full duration of the study. Of the four of these subjects initially assigned to Group A, one moved away from the area, and the other three stopped responding to text messages after multiple attempts. Of the two subjects initially assigned to Group B who did not complete the study, one dropped out after fracturing his leg, and the other stopped because he didn't like the taste of the strip. Of the two subjects initially assigned to Group P who did not complete the study, both cited moving away from the area as their reason for discontinuation.

Table 1. *Demographics by Group*

Group	A	B	P
Age (years)	48 +/- 5.4	55 +/- 6.7	56 +/- 8.1
Race	19-W, 2-B, 3-H	10-W	10-W
Height (cm)	170 +/- 4.2	172 +/- 7.2	171 +/- 5.2
Male	8	3	2
Female	16	7	8
# of Subjects	24	10	10

Note. W = White, non-Hispanic, B = Black, H = Hispanic

Mucoadhesive Strip

The study vehicle is a proprietary mucoadhesive material infused with L-arginine and menthol. According to Squier et al. (2010), menthol has been shown to increase intraoral penetration of several medications, as well as nicotine, while L-arginine applied locally has been shown to enhance vasodilation within the mucosa (Schwedhelm et al., 2008). CBD has been shown to have similar effects with endothelium vasodilation (Stanley et al., 2015).

Mucoadhesive delivery has been developed to enable prolonged absorption at the site of application. Mucoadhesive polymers have many hydrophilic groups, which attach to mucous membranes and cause polymers to swell in water, thus exposing their adhesive sites. This results in enhanced bioavailability and maximum drug concentration in the plasma (Cmax), and decreased time until maximum plasma concentration (Tmax) of the drug (Shaikh et al., 2011).

The THCV and CBD isolates were submitted for independent testing at Salt Leaf Hemp in Vineyard, UT. The THCV isolate was found to contain 999 mg/g of total cannabinoids, no detectable THC, and 959.360 mg/g of THCV. The CBD isolate was found to contain 217.803 mg/g of total cannabinoids, 217.138 mg/g of CBD, and no detectable THC.

RESULTS

Only those subjects who completed the uninterrupted 90 days of use of the intervention were included in the study analysis. The results were evaluated using the placebo group as the

standard for comparison. A one-tailed *p*-value less than .05 was used to determine statistical significance. The Paired Student *t*-test was used to compare before-and-after results within each group. One-way analysis of variance (ANOVA) was used to compare the results of the three different groups. In the tables below, those differences that were statistically significant are provided in bold.

Table 2. *Beginning and Ending Weights (kg), and Abdominal Girths (cm) by Group*

Group	A	B	P
Weight Day 0 (kg)	103.1 +/- 10.9	111.4 +/- 19.1	100.0 +/- 9.4
Weight Day 90	100.4 +/- 10.6	107.3 +/- 19.4	99.0 +/- 9.8
Weight difference	-2.6 +/- 1.5	-4.1 +/- 2.44	-0.1 +/- 1.24
Weight difference T-Test (*p*-value)	**0.001**	**0.004**	0.157
Abdominal girth Day 0 (cm)	117.2 +/- 7.8	123.3 +/- 16.3	113.3 +/- 5.8
Abdominal girth Day 90	112.2 +/- 7.5	119.6 +/- 16.0	111.8 +/- 6.9
Abdominal girth difference	-5.0 +/- 1.3	-3.7 +/- 2.64	-1.45 +/- 1.46
Abdominal girth difference T-Test (*p*-value)	**< 0.001**	**0.011**	**0.041**

Table 3. *Beginning and Ending Blood Pressure Readings by Group in mm Hg*

Group	A	B	P
BP Systolic Day 0	139.9 +/- 8.3	143.3 +/- 18.1	139.5 +/- 13.0
BP Systolic Day 90	131.3 +/- 8.1	131.2 +/- 10.7	137.6 +/- 11.5
Systolic BP difference	-8.7 +/- 5.7	-12.1 +/- 14.2	-1.9 +/- 6.5
Systolic BP difference T-Test (*p*-value)	**0.003**	0.065	0.290
BP Diastolic Day 0	89.9 +/- 6.1	94.8 +/- 10.1	94.1 +/- 8.6
BP Diastolic Day 90	86.5 +/- 5.7	88.8 +/- 7.0	91.5 +/- 9.8
BP Diastolic difference	-3.46 +/- 3.9	-6.0 +/- 8.5	-2.6 +/- 4.0
BP Diastolic difference T-Test (*p*-value)	**0.048**	0.099	0.115

Table 4. *Beginning and Ending Total Cholesterol Levels by Group in mg/dl*

Group	A	B	P
Total Cholesterol Day 0	183 +/- 15.2	196.1 +/- 26.6	178.3 +/- 29.1
Total Cholesterol Day 90	174.2 +/- 12.6	181.4 +/- 30.8	178,7 +/- 24.1
Total Cholesterol difference	-8.8 +/- 11.1	-14.75 +/- 19.0	0.4 +/- 9.9
Total Cholesterol difference T-Test (*p*-value)	0.067	**0.039**	0.469

Table 5. *Beginning and Ending HDL and LDL Levels by Group in mg/dl*

Group	A	B	P
HDL Day 0	48.4 +/- 3.9	53.9 +/- 8.0	53.0 +/- 7.4
HDL Day 90	48.7 +/- 4.2	52.8 +/- 13.3	57.0 +/- 8.7
HDL difference	0.29 +/- 3.0	-1.1 +/- 6.9	4.0 +/- 3.7

HDL difference	0.425	0.380	**0.032**
T-Test (*p*-value)			
LDL Day 0	101.5 +- 12.3	112.0 +/- 18.5	106.5 /- 23.4
LDL Day 90	103.0 +/- 11.1	97.4 +/- 17.2	102.8 +/- 20.2
LDL difference	-7.4 +/- 8.0	-15.5 +/- 7.9	-3.7 +/- 7.5
LDL difference	**0.041**	**0.002**	0.179
T-Test (*p*-value)			

Table 6. *Beginning and Ending Glucose (mg/dl) and A1c (%) Levels by Group*

Group	A	B	P
Glucose Day 0 (mg/dl)	99.5 +/- 7.1	97.6 +/- 3.9	93.5 +/- 3.8
Glucose Day 90	96.7 +/- 5.2	98.5 +/- 3.0	95.3 +/- 9.5
Glucose difference	-2.9 +/- 7.7	0.9 +/- 4.5	1.8 +/- 7.9
Glucose difference	0.235	0.352	0.333
T-Test (*p*-value)			
A1c Day 0 (%)	5.5 +/- 0.2	5.5 +/- 0.1	5.4 +/- 0.2
A1c 90	5.5 +/- 0.2	5.4 +/- 0.2	5.5 +/- 0.2
A1c difference	0.0	0.1	0.1
A1c difference	0.229	0.11	**0.02**
T-Test (*p*-value)			

Table 7. *Comparison of Variance Between Various Groupings*

Student T-Test *p*-values	Group A versus Group B	Group A versus Group P	Group B versus Group P
Weight difference	.157	**.025**	**.003**
Abdominal girth	.183	**.002**	.078
BP Systolic difference	.299	.092	.109
BP Diastolic difference	.272	.400	.242
Total Cholesterol difference	.264	.168	.053
HDL difference	.335	.859	.108
LDL difference	.123	.295	**.024**
Glucose difference	.276	.242	.424
A1c difference	.234	**.015**	**.004**

Table 8. *One Way ANOVA for Factors for all Three Groups*

	One Way ANOVA
Weight difference	F 3.60, p = **.036**
Abdominal Girth	F 3.89, p = **.028**
BP Systolic difference	F 1.09, p = .346
Total Cholesterol difference	F 1.01, p = .374
LDL difference	F 1.28, p = .288
A1c difference	F 4.42, p = **.018**

Exit Interviews and Reporting of Adverse Effects

All subjects were encouraged to report any adverse or unusual effects throughout the 90-day study period. In addition, each of the 44 subjects went through an individual exit interview with the independent physician at the end of the study period to discuss any such effects.

Of the 24 subjects in Group A who were assigned the single dose, 22 (91.7%) reported "no adverse effects." Nine subjects (37.5%) reported that the "taste was somewhat or too strong." One subject (4.2%) reported "feeling like acid in my stomach" after ingesting the strip, and one (4.2%) reported "waking up feeling hungry."

Of the 10 subjects in Group B who were assigned the double dose, 10 (90%) reported "no adverse effects." Four subjects (40%) reported that the "taste was somewhat or too strong." One subject (10%) reported feeling "foggy for the first day."

Of the 10 subjects in Group P who were assigned the placebo, 10 (100%) reported "no adverse effects." All 10g subjects in Group P (100%) reported "no issues."

Urine Drug Testing Results

Nine subjects of the 10 subjects who were using the 16 mg THCV dose daily, all of whom denied any current or previous THC use, consented to participate in urine THC screening on day 90 of the study. Unfortunately, no pre-study urine drug testing was conducted. Seven (77.8%) of the 9 tests administered came back positive. All nine subjects again denied use of THC during the course of the study, suggesting that some of the THCV metabolites excreted in urine will register as THC metabolites on a drug test. The test used was "Home Drug Test Marijuana" by New Choice Inc., with a threshold of 50 ng/ml and a 98% accuracy rate.

Liver Function Study Changes

All 44 subjects underwent liver function studies (alkaline phosphatase, ALP; alanine transferase, ALT; and aspartate aminotransferase, AST) on Day 0 and then again on Day 90 of the study. The ALT levels of all subjects were in the normal range on both Days 0 and 90.

One subject from each group showed very mild elevations above the upper limits of normal (ULN) from the normal range for ALT (normal range: 6-29 U/L). The Group A subject went from an ALT of 18 to 32 U/L. The Group B subject went from an ALT of 22 to 33 U/L, and the Group P subject went from 34 to 37 U/L.

One subject in Group A showed a very mild elevation from the normal range for AST (normal range: 1-35 U/L) to above the ULN, from 20 to 54 U/L.

None of the subjects reported any complaints or exam findings consistent with liver inflammation.

DISCUSSION

Endocannabinoids are orexigenic mediators and are part of the leptin-regulated central neural circuitry that controls energy intake (Di Marzo et al., 2001). Endocannabinoids promote lipogenesis and limit fat elimination in the liver, adipose tissue, and skeletal muscle. The feeling of hunger, mediated by the hypothalamus, is triggered by hormone imbalances such as elevated ghrelin, decreased leptin in circulation, and the binding of 2-AG and AEA to CB_1 receptors (Adams et al., 2005).

Studies have shown that elevated glucocorticoids elevate the expression of endocannabinoids in the regulation of the hypothalamic-pituitary-adrenal axis (Cristino, Becker, & Di Marzo, 2014). Put simply, the chronic, low-grade inflammation that is the hallmark of metabolic syndrome results in chronic elevated appetite, or 'munchies', through elevated endocannabinoid or CB_1 tone, resulting in detrimental metabolic effects.

This study supports THCV, via neutral negative modulation of the CB1 receptor, having anorexigenic effect and CBD, via anti-inflammatory effects through CB2 receptors in the adipose and other tissues, as responsible for the therapeutic metabolic effects documented.

Several animal and human studies (Murphy & Le Foll, 2020) have revealed weight loss and improvement in lipid and diabetic parameters with the use of the selective CB_1 reverse antagonist called Rimonabant or SR141716A (Acomplia, Zimulti; Dol-Gleizes et al., 2009). In a randomized, double-blind rimonabant-placebo

controlled trial, rimonabant showed a notable reduction in body weight among subjects in the groups taking 20 mg of rimonabant daily, with the total amount of weight lost ranging from 2.6 - 6.3 kg per subject. HbA_{1C} in obese patients decreased by 0.5 - 0.6% compared to metformin (Glucophage, Glumetza, Riomet, Glucophage XR, and Fortamet) or sulphonyl urea and by 0.8% compared to a 0.3% reduction in the placebo group (Egan & Colman, 2007).

High-density lipoprotein cholesterol (HDL-C) also increased significantly by 22.3%, compared with 13.4% in the placebo group, while the level of triglycerides decreased in all trials by 6.8%, compared with an increase of 8.3% in the placebo group ($p < .001$). The levels of adiponectin, a protein hormone regulating glucose level and fatty acid breakdown in humans, increased significantly by 23% from the baseline in the rimonabant group (Abioye et al., 2020).

Unfortunately, earlier studies did not take into account the fact that endocannabinoid tone is controlled by 'on demand' release, versus CB_1 receptor activity, which is always active (Howlett et al., 2011). The inverse antagonist rimonabant had severe psychiatric effects, postulated to be due to suppression of the innate constitutive activity of the CB_1 receptors in the brain. Rimonabant was never approved by the FDA, and it was taken off the market shortly after its release in Europe (Abioye et al., 2020). Recent preclinical studies suggest that neutral, instead of inverse, antagonists of the CB_1 may retain the therapeutic potential of Rimonabant, without the adverse effects (Murphy & Le Foll, 2020).

Weight Loss

A review of the results in Table 2 reveals that 16 of the 24 subjects in Group A lost weight over the 90-day period. The average weight loss was 2.6 kg +/- 1.5 kg ($p = .001$), and the greatest weight loss was 11.1 kg . Seven out of 10 subjects in Group B lost weight. The average weight loss was 4.1 kg +/- 2.44 kg (p = .004), and the greatest weight loss was 13.95 kg. Over a 30-day period, this equates to an average weight loss of 0.86 kg for Group A and 1.36 kg for Group B, consistent with prior unpublished studies using 50 mg of Hempson Oil® gel caps daily.

Table 7 reveals a statistically significant difference between Group A and Group P, as well as Group B and Group P, for weight loss ($p = .002$). There was almost a statistically significant difference between Group B and Group P ($p = .078$) for abdominal girth.

One-way ANOVA in Table 8 revealed statistically significant differences in body weight difference from Day 0 to Day 90 across the three groups ($p = .036$).

Abdominal Girth

A review of the results in Table 2 reveals that 23 of the 24 subjects in Group A showed a decrease in abdominal girth from Day 0 to Day 90 of the study. The greatest girth loss in Group A measured at 12.6 cm, while the average loss across Group A was 5.0 cm +/- 1.3 cm ($p < .001$).

Seven out of 10 subjects in Group B showed a decrease in abdominal girth; the greatest decrease in girth from Group B measured 13.0 cm. The average decrease across Group B was 3.7 cm +/- 2.64 cm ($p = .011$).

Over a 30-day period, this equates to an average abdominal girth loss of 1.67 cm per month for Group A, and 1.23 cm per month for Group B, consistent with prior unpublished studies using 50 mg of Hempson Oil® gel caps daily.

It is interesting to note that there was a barely statistically significant decrease in abdominal girth in the control/placebo group (Group P); however, it is also worth noting that abdominal girth is probably the least accurate of all the biometric measurements taken for the purposes of this study.

Table 7 reveals a statistically significant difference between Group A and Group P ($p = .003$) respectively.

One-way ANOVA in Table 8 revealed statistically significant differences in abdominal girth differences from Day 0 to Day 90 among the three groups ($p = .028$).

Systolic Blood Pressure

A review of Table 3 reveals that only Group A showed statistically significant differences in blood pressure, with 17 out of 24 showing a decrease in systolic and 15 out of 24 showing a decrease in diastolic blood pressure. The greatest decrease was 29mm Hg in systolic and 21mm Hg for diastolic blood pressure, while the average decrease was 8.7mm Hg +/- 5.7mm Hg ($p = .003$)

in systolic and 3.46mm Hg +/- 3.9mm Hg in diastolic blood pressure (p = .048). Although not statistically significant, 7 out of 10 subjects in group B had decreased systolic blood pressure and 5 out of 10 had decreased diastolic blood pressure, with the average diastolic blood pressure decreasing 12.1mm Hg +/- 14.2mm Hg (p = .065). This result is consistent with prior unpublished studies using Hempson Oil.®

Total Cholesterol

A review of Table 4 reveals a statistically significant difference in total cholesterol levels in Group B of -14.75 mg/dl +/- 19.0 mg/dl (p = .039). The difference in group A, -8.8 mg/dl +/- 11.1 mg/dl (p = .067), almost reached statistical significance, consistent with the previously unpublished studies that revealed a decrease in total cholesterol seen with 50 mg of daily Hempson Oil® administration.

HDL and LDL Cholesterol

A review of Table 5 reveals statistically significant differences in only LDL for Group A, -7.4 mg/dl +/- 8.0 mg/dl (p = .041), and also for Group B, -15.5 mg/dl +/- 7.9 mg/dl (p = .002). This is consistent with the decrease in total cholesterol seen in previously unpublished studies on Hempson Oil®.

In the HDL comparison, there was an unexpected statistically significant difference in Group P levels, probably due to the small sample size.

Blood Sugar and A1c

Review of Table 6 reveals no statistically significant differences in blood sugar or A1c percentages across all groups. This is in contrast with prior studies that have suggested a modest effect of THCV on decreasing blood sugar and A1c, as well as prior unpublished studies utilizing high-CBD, THCV, and CBDV Hempson Oil®.

Table 7 reveals no statistically significant difference between Group A and Group B, but statistically significant differences between Group A and Group P, and Group B and Group P (p = .015 and p = .004, respectively). The one-way ANOVA also revealed statistically significant differences from Day 0 to Day 90 among the three groups (p =.018), again suggesting that small sample size may have hindered the assessment of A1c effects in this study.

Positive Urine THC Drug Screening

Seven out of the nine subjects in Groups A or B who submitted urine for THC testing tested positive, despite never using THC in their lives. This suggests that long-term daily consumption of 8 -16 mg-dose THCV isolate is likely to register a positive result on a THC screening test, due to the presence of THC metabolites in THCV isolates. Anyone using THCV should be advised of this possibility.

Liver Function Testing

Mild ALT and AST elevations are the most frequent abnormalities seen in asymptomatic persons (Swarup et al., 2022). Between one and four percent of healthy adults have elevated transaminases (Sidibeh et al., 2017).

One out of 24 (4.1%) subjects in Group A and one out of 10 (10%) subjects in Group B had very mild elevations of ALT. A separate subject (8.3%) in Group A had a very mild elevation in AST between Day 0 and Day 90. These subjects were advised to schedule a follow-up with their primary care physician to explore potential causation for these elevated levels. Potential causes of transient liver transaminase elevations include viral hepatitis, alcohol use, medication use, steatosis or steatohepatitis, and cirrhosis; obesity, hyperlipidemias and diabetes mellitus are associated with elevated ALT and AST (Swarup et al., 2022). Unfortunately, we did not track subjects' alcohol consumption, certain medications, or other potential causes of increased ALT and AST over the course of the study.

Animal studies on THCV have failed to reveal any issues with elevated transaminases (Pekgor et al., 2019). A study of very high doses (1500 mg/day) of CBD in healthy adults revealed that 7 out of 16 (44%) experienced peak serum alanine aminotransferase (ALT) values greater than the upper limit of normal (ULN; Fujita et al., 2006). For five (31%) subjects, the value exceeded five times ULN, therefore meeting the international consensus criteria for drug-induced liver injury. There was no correlation between transaminase elevations and baseline characteristics, CYP2C19

genotype, or CBD plasma concentrations. All ALT elevations above the ULN began within 2-4 weeks of initial exposure to CBD. Of the six subjects with ALT elevations who were discontinued from the protocol, some had symptoms consistent with hepatitis or hypersensitivity.

A review of available studies stated,

> "There is a low probability of serious hepatotoxicity at the high therapeutic doses [of CBD]… and a much lower risk of adverse hepatic effects and a potential for hepatoprotection effects at the lower doses commonly used in dietary supplements and food products… studies have addressed the safety, including hepatotoxic potential of, the CBD drug product Epidiolex® in conjunction with its efficacy in seizure and psychotic disorders. All the studies were confounded by concomitant use of antiepileptic medications, especially valproic acid, known to be associated with elevated transaminases" (Stohs & Ray, 2020).

Subject recruitment was limited by the ongoing COVID-19 epidemic. Due to a limited number of subjects in Group B compared to Group A, statistical power was lowered, limiting study results. Some statistically significant associations may have been missed due to the limited number of subjects in Groups B (10) and P (10) compared to Group A (24.) Even so, the study revealed several clinically significant findings consistent with prior pre-clinical and unpublished human studies.

Conclusion

In summary, 90 day use of once-daily THCV and CBD-infused mucoadhesive strips was associated with clinically significant weight loss, decreases in abdominal girth, systolic blood pressure, and total and LDL cholesterol. While the study was limited by small sample sizes in both the high dose and placebo groups, overall results suggest positive effects on A1c levels.

The 16 mg/20 mg daily dose in Group B was superior for weight loss compared to the 8 mg/10 mg daily dose in Group A. The results of this study for weight loss, abdominal girth loss, and decreases in cholesterol were congruent with the prior unpublished studies of Hempson Oil®, a hemp extract high in THCV, CBDV, and CBD. Ninety days of daily use of 16 mg of THCV were associated with a false-positive urine drug test for THC, as well as a small risk of very mild elevations of ALT or AST compared to placebo.

Future studies should control for risk factors for common transient elevations of transaminases seen with binge or excessive alcohol use or certain other medications. In addition, all subjects should have pre- and post-study urine drug testing for THC metabolites to more effectively address the question of falsely positive urine drug testing.

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