Research Protocol

General Information

Protocol Title: Acute Effects of Cannabigerol

Protocol Number: NCT05257044

***Protocol Registration Location and Date*:** clinicaltrials.gov (25/02/2022)

Document Date: *August 10, 2024*

Project Summary

Cannabigerol (CBG) is a phytocannabinoid increasing in popularity, with preclinical research indicating it has anxiolytic and antidepressant effects. However, there are no published clinical trials to corroborate these findings in humans. Therefore, the primary objective of this study is to examine the acute effects of CBG on anxiety, stress, and mood. Secondary objectives are to examine whether CBG produces subjective drug effects or motor and cognitive impairments. We will assess these objectives using a double-blind, placebo-controlled cross-over field trial with 34 healthy adult participants with experience using cannabis. Participants will complete two sessions (with a one-week washout period) via Zoom. In each, they will provide ratings of anxiety, stress, mood, and subjective drug effects prior to double-blind administration of 20mg hemp derived CBG or placebo tincture (T0). These ratings will be collected again after participants orally ingest the product and complete an online survey (T1), again after they complete the Trier Social Stress Test (T2), and again after they complete a verbal memory test and the DRUID impairment app (T3). We hypothesize that CBG will decrease anxiety, decrease stress, and elevate mood. Further, we hypothesize that ratings of subjective drug effects will be low and that CBG will not produce motor or cognitive impairments.

Rationale and Background

The rapid proliferation of the new legal cannabis market has instigated producers to cultivate an array of novel products to satisfy consumers' growing interest. While products high in delta-9-tetrahydrocannabinol (THC) continue to saturate the market [1], a growing body of consumers are seeking alternative non-intoxicating products carrying the promise of easing what ails them. Producers are responding to this demand by isolating various minor phytocannabinoids and marketing them with bold, but largely unsubstantiated, claims of their therapeutic potential. While cannabidiol (CBD) continues to be the dominant non-intoxicating cannabinoid of interest to both consumers and researchers, cannabigerol (CBG) is rapidly increasing in popularity [2].

CBG is a minor phytocannabinoid that is often referred to as "the mother of all cannabinoids" as it is a precursor to numerous other phytocannabinoids, including THC, CBD, and cannabichromene (CBC). CBG received little research interest initially, due in part to the overwhelming focus on the effects of THC and CBD. Subsequent pre-clinical investigations involving the administration of CBG to animals, however, have demonstrated a broad spectrum of potential therapeutic effects including potent antibiotic [3] and antifungal activity [4]. CBG also appears to have anti-hypertensive effects [5], it reduces intra-ocular pressure [6] and keratinocytes in a psoriasis model [7], it has possible efficacy in inflammatory bowel disease [8] and it may have analgesic effects [9]. Moreover, CBG has been demonstrated to have antidepressant-like effects in rodent tail suspension model [10] while lacking cannabimimetic effects indictive of THC [10,11].

In stark contrast to the impressive body of preclinical research, there has been a dearth of research examining the effects of CBG on humans. To help fill this gap, we recently published a study in which 127 experienced CBG users were surveyed on their use of CBG-dominant products, including their use patterns, the perceived therapeutic effects of CBG, as well as its potential side effects [12]. Participants most frequently reported using CBG to manage anxiety (attested to by 51% of the sample), chronic pain (41%), depression (33%), and insomnia (31%). Moreover, most of the sample indicated that CBG was more effective than conventional medications for treating depression (80%), anxiety (78%), chronic pain (74%), and insomnia (73%). Only a minority reported experiencing side effects such as dry eyes (9%), dry mouth (16.5%), sleepiness (15%), and increased appetite (12%). While provocative these findings are limited by their retrospective, self-

report, nature, and the use of preparations of varying CBG composition. As such, they require corroboration via double-blind, placebo-controlled clinical trials. However, to date there are no published clinical trials on the effects CBG in humans.

Study Goals and Objectives

The goal of the present study is to examine the effects of CBG on humans using a rigorous double-blind, placebo-controlled cross-over trial. The primary objective is to investigate the acute effects of CBG on self-reported anxiety, stress, and mood. The secondary objectives are to assess subjective drug effects (intoxication, drug effect, drug liking), potential side effects (dry eyes, dry mouth, sleepiness, appetite, racing heart/heart palpitations) as well as to determine whether CBG produces motor or cognitive impairments.

Study Design

Design: A double-blind, placebo-controlled cross-over field trial will be used to address our primary and secondary objectives.

Inclusion Criteria*:* Aged 21 years or older; reside in Washington State; have a smartphone and have access to a computer with a webcam connected to stable internet in a private environment; fluent in English; able to see, hear, and read; prior experience with cannabis-based products (i.e., ≥10 lifetime uses, use in the past month); willing to abstain from using products containing cannabis or CBG for a minimum of 24 hours prior to the testing session.

Exclusion Criteria: Chronic neurological disorders; head injuries involving a loss of consciousness for more than 10 mins; diagnosed intellectual disorder, psychotic disorder, autism spectrum disorder, or bipolar disorder; pregnant or breastfeeding; illicit drug use (except cannabis) in the past 2 months; serious prior adverse reactions to CBG (e.g., panic attacks, psychosis).

Methodology

Recruitment: Participants will be recruited using advertisements posted in cannabis dispensaries, at Washington State University, in the community, and on social media as well as by emailing cannabis users who had completed our other lab studies. Prospective participants will be directed to complete a brief online Qualtrics screening survey that includes bot detection and contains questions probing the various inclusion/exclusion criteria reported above.

Pre-testing Session: Eligible participants will be invited to a pre-testing Zoom session with either the principal investigator (PI) or a research assistant (RA) to ensure they can access Zoom on a secure stable internet connection in a personal environment and obtain informed consent. After obtaining consent they will download the DRiving Under the Influence of Drugs (DRUID) app and complete its baseline trials. The benchmark version of this mobile application contains four brief tasks (each under 45 sec), completed on a smartphone, that measure cognitive and motor impairment. Prior to completing the tests, participants will be instructed to stand up and hold their phone in one hand and tap the screen with their other hand. For the first task, circles and squares briefly flash on the screen and participants are instructed to tap the location on the screen where each circle flashed and to tap a white oval at the top of the screen whenever they see a square, as quickly as possible. The instructions change mid-way through the task and participants are instructed to tap the location on the screen where each *square* flashed and to tap the white oval at the top of the screen whenever they see a *circle,* as quickly as possible. For the second task, circles briefly appear on the screen, and participants are instructed to tap where they saw each circle as

quickly as possible and to press STOP at the top of the screen when they have estimated that 30 secs have passed. For the third task, participants are instructed to keep their finger on a moving circle and count the number of squares that briefly appear on the screen. For the fourth task, participants are instructed to raise their left foot off the floor and balance on their right foot while holding their phone in their left hand for 15 sec. Finally, they switch sides and raise their right foot off the floor while holding their phone in their right hand for 15 sec. The primary outcome measure from this app is a global impairment score, with higher scores indicating more motor and cognitive impairment.

After completing three baseline trials of the DRUID app participants will schedule their testing sessions. The PI or RA will assign their ID code (sequentially) and will provide the participant with contact information of a CBG producer who will ship color-coded vials of hemp derived CBG and placebo directly to them. Finally, participants will be instructed to abstain from using any cannabis products including CBG for a minimum of 24 hours prior to their testing session.

Testing Sessions: Approximately one-week after the pre-testing Zoom session, participants will meet with a RA (blinded to the color-codes used for the drug and placebo) on Zoom for their first testing session. First, the RA will confirm that participant has abstained from use of cannabis or CBG for a minimum of 24 hours prior to the testing session. As depicted in Figure 1, participants will then provide baseline (T0) ratings of their subjective state (anxiety, stress, mood). Specifically, participants will rate their subjective levels of anxiety and stress using 0 (not at all) to 10 (extremely) visual analogue scales, and they will rate their subjective mood using a 0 (extremely negative) to 10 (extremely positive) visual analogue scale. They will also complete the state form of the State-Trait Anxiety Inventory, which assesses symptoms of anxiety participants are experiencing in the moment [12].

Next, participants will be instructed to ingest one of the color-coded vials. Half the participants (those assigned odd ID codes) will be assigned to ingest the blue vial containing 20mg CBG first and the other half (those assigned even ID codes) will be assigned to ingest the yellow vial containing 20mg placebo first. The CBG tincture is composed of 10 mg/ml CBG, 0.89 mg/ml CBGA, beta-caryophyllene 0.35 mg/ml (0.51 mg/ml total terpenoids). It is derived from a CBG-dominant hemp plant containing less than the 0.3% THC limit imposed in the U.S. Agricultural Improvement Act of 2018. Single 3ml amber vials will be prepared with this material containing 2ml each representing a dose of 20mg of CBG. Chartreuse liqueur (55% ethanol by volume) prepared by Les Peres Chartreux, France 1ml, diluted with 1ml filtered water will be employed as the placebo as it provided a reasonable match for the green color and herbal/ethanol taste of the CBG tincture. Opaque vials will be labeled with color coded tabs (Blue = CBG, Yellow = Placebo) in double-blind fashion and mailed directly to study participants. To dilute the taste, participants will be instructed to mix the contents of the vial in a small glass of water prior to ingestion.

After observing the participant orally ingest the product, the RA will instruct them to complete an online survey that contains measures of their demographic characteristics; anxiety, depression, and stress levels; as well as their cannabis and CBG use patterns. Specifically, participants will be asked to provide information pertaining to their gender, age, ethnicity, education, personal income, work status, and marital status. They will also complete the Daily Sessions, Frequency, Age of Onset, & Quantity of Cannabis Use Inventory (DFAQ-CU) which is a 41-item inventory, with 24 core items that assess frequency, age of onset, and quantity of cannabis flower, quantity of cannabis concentrates, and quantity of edibles typically used [13]. The remaining items measure other aspects of cannabis use not commonly measured by other cannabis use scales (e.g., forms of cannabis; methods of administration; use for medical, recreational, or combined purposes). The

online survey will also contain the State-Trait Anxiety Inventory (STAI) which measures state and trait anxiety [12]. The inventory contains two parts, one containing 20 items designed to assess state anxiety and another part containing 20 items designed to assess trait anxiety. The state anxiety section assesses how individuals feel in the moment, while the trait anxiety section assesses how individuals generally feel. Finally, participants will complete the Depression Anxiety Stress Scales (DASS-21) which will be used to assess levels of depression, anxiety, and stress [14]. Each of the three subscales contains seven statements and participants indicate how much each statement has applied to them in the past week.

After completing the online questionnaire, participants will provide T1 ratings of their subjective state and subjective drug effects. Specifically, participants will rate their subjective levels of anxiety and stress using a 0 (not at all) to 10 (extremely) visual analogue scales, and they will rate their subjective mood using a 0 (extremely negative) to 10 (extremely positive) visual analogue scale. They will also complete the state form of the STAI. They will rate their levels of intoxication using a 0 (not at all intoxicated) to 10 (extremely intoxicated) visual analogue scale, the level of drug effects they were experiencing using 0 (none) to 10 (a lot) visual analogue scale, and their liking of the drug effects using 0 (dislike very much), 5 (neutral) to 10 (like very much) visual analogue scale. They will also rate their level of dry eyes, dry mouth, sleepiness, appetite, and racing heart/heart palpitations using 0 (none) to 10 (extremely) visual analogue scales. The approximate time between T0 and T1 ratings will be 20 mins.

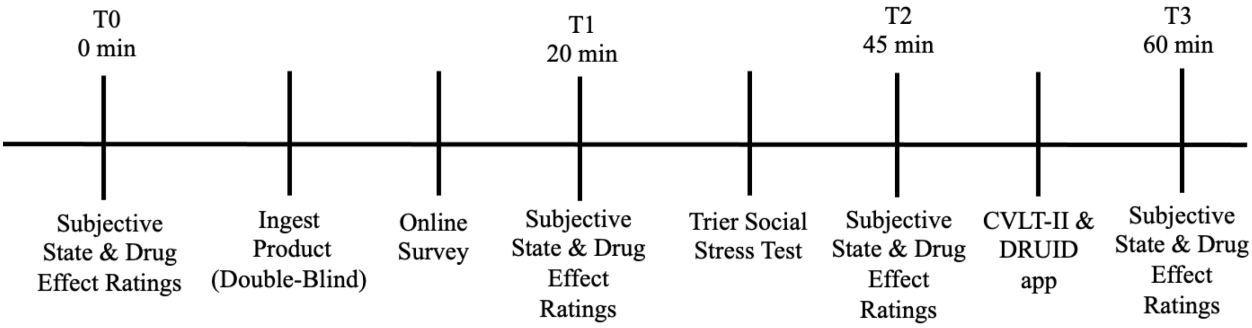
Participants will subsequently complete the online Trier Social Stress Test (TSST) [15]. For this task, participants will be instructed to mentally prepare a 5-min speech describing why they would be a good candidate for their ideal job. They will be informed that the speech will be recorded and reviewed by a panel of judges trained in public speaking (although no such recording will be made). They will be sent to a Zoom breakout room for 10-mins to prepare their speech. The RA will put on a white lab coat while they are in the breakout room. Participants will be brought back to the main Zoom room and asked to deliver their speech to the RA who will maintain a neutral expression. They will be instructed to speak for the entire 5-min period and will be prompted to continue if they stop for more than 20 secs. Immediately upon completing the speech, they will be told they will need to complete a 5-min math test. For this test, they will be instructed to sequentially subtract the number 13 from 1,022. Each time they make a mistake they will be informed they made a mistake and will be instructed to start over from 1,022. Following the stress manipulation, participants will provide T2 ratings of their subjective state and subjective drug effects as described above. The mean time between T0 and T2 ratings will be approximately 45 mins.

Participants will then complete the California Verbal Learning Test-II (CVLT-II) [16] which assesses verbal free recall. Participants will be asked to listen to and immediately recall a list of 16 words three times in a row (Trials 1–3). They will then be asked to listen to and immediately recall a list of 16 new words (List B). Immediately following recall of List B, participants will be required to recall the words from List A (Short Delay). Alternate forms of the lists will be used in the first and second testing sessions to reduce practice effects. Immediately after completing the CVLT-II participants will complete the DRUID app. Finally, participants will provide T3 ratings of their subjective state and subjective drug effects as described above. The mean time between T0 and T3 ratings will be approximately 60 mins.

One-week after the first testing session, participants will complete the second testing session. This session will be identical to the first testing session except those participants who ingested the blue vial containing CBG in the first session, will ingest the yellow vial containing placebo in the second session. Those who ingested the yellow vial containing placebo in the first session, will ingest the

blue vial containing CBG in the second session. Neither the participant nor the RA will know which color code corresponds to CBG and placebo.

Figure 1. Overview of Procedure for Each Testing Session



Safety Considerations

Risks of physical harm, discomfort, and psychological distress will be minimized by only recruiting individuals who have experience using cannabis-based products (have used these products at least 10 times) and by informing participants that they can skip questions they are not comfortable answering and cease tests they are not comfortable continuing. Our prior survey study on CBG indicates that CBG does not cause serious adverse reactions with only a minority of participants indicating they experience minor side effects (dry eyes, dry mouth, increase appetite, increased heart rate etc.). Nevertheless, participants who experience psychological distress will be provided with information about crisis lines and counseling services. If participants report any serious side effects from the CBG we will submit an adverse event report to the IRB and will cease further testing until guidance is provided from the IRB.

Follow-up

There are no plans to follow-up on participants unless they experience an adverse event.

Data Management and Statistical Analyses

Data Management: Data will be stored in a locked private office and on password protected encrypted computers. Prescreening data and survey data will be stored on Qualtrics and then downloaded onto a password protected encrypted computer. The Master list (linking ID codes to individual participants) will be stored on the PIs password protected encrypted WSU owned computer. The RA will enter the data into Excel on a password protected computer and data entry will be checked by an independent RA and/or the PI.

Power: Results of an a priori power analysis using G-Power indicate that a sample size of 34 will be required to achieve power of .80 to detect medium-sized effects (i.e., d = 0.50), with alpha set at .05.

Data Analysis Plan*:* Pairwise deletion will used to handle the small amount of missing data anticipated. Alpha will be set to .05 and effect sizes of 0.01 will be interpreted as small, 0.06 will be considered medium, and 0.14 and above will be considered large. Data will be analyzed using IBM SPSS v.27.

Percentages, means, and standard deviations will be used to determine the demographic characteristics and cannabis use patterns of the sample. Mean DASS subscale scores, mean subjective state (mood, anxiety, stress) ratings, mean STAI state and trait anxiety scores, and mean

subjective drug effect ratings will be computed at baseline (T0) for each condition.

Change scores will be created by subtracting baseline (T0) scores from T1, T2, and T3 scores for the subjective state ratings (anxiety, stress, mood), STAI state anxiety scores, and subjective drug effect ratings (dry eyes, dry mouth, sleepiness, appetite, heart palpitations/racing heart).

Primary Outcomes: To assess the primary outcome (determine the effects of CBG vs. placebo on anxiety, stress, and mood) a series of 2 x 3 repeated-measures ANCOVAs will be conducted with condition (CBG, placebo), and time (T1, T2, T3) as within-subjects factors, order of drug administration as a covariate, and changes (difference from T0 to T1, T2, T2) in ratings of anxiety, stress, and mood as separate dependent variables.

Secondary Outcomes: To assess the effects of CBG on subjective drug effect ratings (dry eyes, dry mouth, sleepiness, appetite, heart palpitations/racing heart) a series of 2 x 3 repeated-measures ANCOVAs will be conducted with condition (CBG, placebo), and time (T1, T2, T3) as within-subjects factors, order of drug administration as a covariate, and changes (difference from T0 to T1, T2, T2) in these subjective drug effect ratings as the dependent variables.

To determine the effects of CBG vs. placebo on intoxication, drug effect, and drug liking ratings a series of 2 x 3 repeated-measures ANCOVAs will be conducted with condition (CBG, placebo), and time (T1, T2, T3) as within-subjects factors, order of drug administration as a covariate, and ratings of each indicator of drug effects as the dependent variables.

To examine the acute effects of CBG on verbal memory, a 2 x 5 repeated-measures analysis of covariance (ANCOVA) will be conducted with condition (CBG, placebo), and CVLT-II trial (Trial 1, Trial 2, Trial 3, Trial 1B, Short-Delay) as within-subjects factors, order of drug administration as a covariate, and number of words correctly recalled as dependent variable.

Finally, to assess the effects of CBG vs. placebo on impairment, a one-way repeated measures ANCOVAs will be conducted to compare DRUID scores at baseline, in the CBG condition, and in the placebo condition, while controlling for order.

Expected Outcomes

CBG is increasing in popularity, with many individuals claiming this non-intoxicating legal substance has medicinal properties and effectively reduces anxiety, depression, pain, and symptoms of other medical conditions. While a small body of pre-clinical rodent studies support these claims currently no objective human research on the potentially beneficial or detrimental effects of CBG exists. As such, this will be the first objective examination of the potentially beneficial and detrimental effects of CBG on humans. Results will help to inform current and potentially future CBG users on its potential risks and benefits.

Dissemination of Results

Results will be disseminated at scientific conferences (e.g., International Cannabinoid Research Society, Gordon Research Conference) and in a scientific journal (https://www.nature.com/articles/s41598-024-66879-0). A press release will be issued by the PI's university following publication. Dr. Cuttler will be first author, Amanda Stueber will be second author, Ziva Cooper will be third author, and Ethan Russo will be last author.

Duration of the Project

Recruitment, testing, data entry, data analysis, and preparation of the manuscript are anticipated to require 2 years.

Problems Anticipated

There are no anticipated problems.

Project Management

Dr. Cuttler will train research assistants, oversee data collection, check the data for data entry errors, analyze the data, and prepare the manuscript.

Amanda Stueber will advertise the study, helped collect and enter data, helped interpret the results, and help prepare the manuscript.

Dr. Cooper and Dr. Russo assisted Dr. Cuttler in designing the study and will help prepare the manuscript.

Ethics

Anticipated risks are low but may include risk of invasion of privacy and breach of confidentiality. These risks will be minimized by using ID codes to identify participants and their data. Only the PI will retain a master list connecting these ID codes to participants' identities. Further all study personnel will sign confidentiality agreements. Moreover, participants will be asked to schedule their Zoom testing session during a time when other individuals are not around them. Risks associated with a single dose of CBG are also considered low given low reports of adverse reactions to CBG and screening of those who have experienced serious adverse reactions to the drug.

Approval from the Institutional Review Board at Washington State University will be received prior to any data collection. All participants will provide informed consent during the pre-testing session. During this session, participants will be directed to a Qualtrics survey that will contain the complete written consent form (see below). The RA will review the major points of the consent form with them and then will request that they read the consent form. Participants will be informed that they are under no obligation to complete the study and that they are free to withdraw at any time without consequence (aside from loss of compensation). Participants will be asked if they have any questions, and the RA will answer all questions. Participants will then be asked to click the "I agree" option at the bottom of the consent form if they consent to participating in the study.

Results (Primary Outcomes)

Subjective Anxiety, Stress, Mood

A 2 x 3 repeated-measures ANCOVA on changes in subjective anxiety ratings (changes from T0 to T1, T2, T3) revealed a moderately large-sized statistically significant main effect of condition, $F(1, 32) = 4.88$, $p = .034$, eta = .132, and a large-sized statistically significant main effect of time, $F(2, 64) = 7.76$, $p < .001$, eta = .195. The interaction between condition and time was small in magnitude and was not statistically significant, $F(2, 64) = 1.56$, $p = .217$, eta = .047. The main effect of condition reflects overall larger reductions in self-reported feelings of anxiety in the CBG condition compared to the placebo condition.

A 2 x 3 repeated measures ANCOVA on changes in subjective stress ratings revealed a large-

sized statistically significant main effect of time, $F(2, 64) = 8.20$, $p < .001$, eta = .204, and a small-sized main effect of condition that was not statistically significant, $F(1, 32) = 1.19$, $p = .283$, eta = .036. This main effect of time was qualified by a moderately large-sized statistically significant interaction between condition and time, $F(2, 64) = 4.90$, $p = .011$, eta = .133. Probing of this interaction revealed a moderately large-sized simple effect of condition on change in subjective stress ratings at T1, $F(1, 32) = 5.02$, $p = .032$, eta = .136. In contrast, there were no significant differences in changes in stress ratings in the CBG and placebo conditions at T2, $F(1, 32) = 0.31$, $p = .583$, eta = .010, or T3, $F(1, 32) = 2.26$, $p = .142$, eta = .066.

The 2 x 3 repeated measures ANCOVA on changes in subjective mood ratings revealed no significant main effects of time, $F(2, 64) = 2.56$, $p = .085$, eta = .074, or condition, $F(1, 32) = 3.25$, $p = .081$, eta = .092, and no condition x time interaction, $F(2, 64) = 2.27$, $p = .111$, eta = .066.

Verbal Memory

A 2 x 5 repeated measures ANOVA with condition (CBG, placebo) and trial as within-subjects factors and order as a covariate revealed a moderate-sized effect of condition that was statistically significant, $F(1, 30) = 4.17$, $p = .050$, eta = .122 and a large-sized effect of time that was statistically significant, $F(4, 120) = 70.14$, $p < .001$, eta = .700. The interaction between condition and time was small and not statistically significant, $F(4, 120) = 0.38$, $p = .820$, eta = .013. Verbal memory test performance was significantly better in the CBG condition.

DRUID Impairment

The one-way repeated measures ANCOVA on DRUID impairment scores revealed a small sized effect of condition that was not statistically significant, $F(2, 64) = 0.76$, $p = .474$, eta = .023.

Complete results can be found in the published manuscript:

https://www.nature.com/articles/s41598-024-66879-0

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WASHINGTON STATE UNIVERSITY
Department of Psychology

Research Study Consent Form

Study Title: Acute Effects of Cannabigerol (CBG)

Researchers:

Principal Investigator: Dr. Carrie Cuttler, Assistant Professor, Department of Psychology, 509-335-0681

Co-Investigators: Amanda Stueber, Graduate Student, Department of Psychology; Aria Petrucci, Graduate Student, Department of Psychology

Sponsor: CReDO Science provided the funding for this study.

KEY INFORMATION ABOUT THIS STUDY

Your consent is being sought for research. Participation is voluntary.

Study Purpose – This study is being conducted to examine the acute effects of cannabigerol (CBG) on mood, anxiety, stress, and cognition, as well as to explore some of its potential side effects (e.g., dry eyes).

Major Activities of Subject Participation – You will be asked to complete two testing sessions. During one session, you will be asked to ingest 20 mg of CBG tincture orally and during the other you will be asked to ingest a placebo. During both sessions, you will complete non-invasive tests of your cognition, mood, and stress over Zoom videoconferencing software. You will also be asked to prepare and deliver a brief speech and do mental math.

Duration of Participation – The study will require approximately 3 hours to complete.

Significant Risks – Potential risks include potential physical and psychological discomfort as a result of ingesting CBG; answering questions about your mood, anxiety, and stress; completing cognitive tests; and delivering a speech. There is also a small risk of potential invasion of privacy and breach of confidentiality.

Potential Benefits – There are no direct benefits to you from being in this study.

What you should know:

You are being asked to take part in a research study carried out by Dr. Carrie Cuttler, Amanda Stueber, and Aria Petrucci. This form explains the research study and your part in it if you decide to join the study. Please read the form carefully, taking as much time as you need. Ask the researcher to explain anything you do not understand. Your participation in the study is voluntary. You can decide not to join the study. If you join the study, you can change your mind later or quit at any time. You may refuse any question, test, or procedure. There will be no penalty or loss of services or benefits if you decide to not take part in the study or quit later. This study has been registered on clinicaltrials.gov and has been approved for human subject participation by the Washington State University Institutional Review Board.

What is the purpose of this study?

This research study is being done to examine the acute effects of CBG on mood, anxiety, stress, and cognition. We are also interested in exploring potential minor side effects of CBG (e.g., dry mouth). This is a clinical trial, not a treatment. You are being asked to take part because you use CBG products.

You cannot take part in this study if you are under the age of 21, have present or past history of psychosis, autism, bipolar I disorder, or an intellectual disability. You are not eligible to participate if you are pregnant or breastfeeding, are not fluent in English, are illiterate, blind, or deaf. You cannot participate if you have used any illicit drugs in the past 2 months. Individuals who have used cannabis-based products less than 10 times or who have had a serious adverse reaction to cannabis-based products are not eligible to participate. To participate, you must have access to a private environment (e.g., your home) where you have access to a computer with a webcam connected to high-quality and stable internet.

What will I be asked to do if I am in this study?

If you take part in the study, you will be asked to complete two 90-minute testing sessions. Before the first testing session you will need to obtain a small amount of CBG and placebo directly from a distributor who will provide these study materials to you free of charge. You will also need to abstain from CBG and use of any product containing cannabis for a minimum of 24 hours prior to your testing session. During one testing session you will be asked to ingest 20 mg of CBG orally and during the other you will be asked to ingest a placebo. Neither you nor the RA will know which substance you are ingesting (only the PI will have this knowledge). You will also be asked to complete an online survey via Qualtrics. The survey will contain demographic questions as well as questions about your cannabis use patterns, mood, anxiety, and stress. You will be asked to complete cognitive tests that will be administered over Zoom videoconferencing by the research assistant as well as via a free app called DRUID that you will be asked to download and install on your smartphone. The cognitive tests you will complete are non-invasive tests of your memory (e.g., remembering lists of words), attention and motor skills (responding with appropriate keyboard clicks to basic stimuli). Finally, you will be asked to prepare and deliver a brief speech and perform mental math in front of the research assistant. Taking part in both testing sessions will take about 3 hours. We will enroll approximately 34 participants in this study.

Are there any benefits to me if I am in this study?

There is no direct or intended benefit to you from being in this study aside from being exposed to the scientific process and potentially learning more about that process and about CBG.

If you take part in this study, you will advance scientific knowledge on the potentially beneficial and detrimental effects of CBG on humans.

Are there any risks to me if I am in this study?

The potential risks from taking part in this study are a breach of confidentiality, invasion of privacy, as well as physical and/or psychological distress. For instance, potential risks include potential discomfort as a result of CBG or answering questions (e.g., “I hate myself”), taking cognitive tests, and preparing and delivering a short speech. To minimize the risk of discomfort, only experienced

CBG-users are invited to participant, and you may skip questions in the survey and refuse to complete any tests or procedures. Further, to minimize the risks of an invasion of privacy you were asked to schedule the Zoom call when you have access to a secure personal environment where others will not be in the vicinity. To minimize the risk of a breach of confidentiality the survey data will be housed in a cloud-based platform behind high-end firewalls and all transmitted data will be encrypted and we will use Zoom videoconferencing software which uses end-to-end encryption and no recordings of videoconferencing sessions will be made by the research team or by Zoom. Only the principal investigator and co-investigators will have the password to access these online data. The remaining data you provide will be stored on a password protected, encrypted computer and a filing cabinet in The Health & Cognition Lab directed by Dr. Cuttler. All research personnel involved in the study have signed confidentiality agreements.

As with any experimental procedures, there may be adverse events or side effects that are currently unknown. Testing may be ceased at any time if you are unable to or do not wish to continue. Furthermore, if you disclose any information which disqualifies you from participating during the study (e.g., history of psychosis, serious neurological conditions, residence outside Washington State etc.), testing may be ceased, and you will be given a prorated amount of compensation for your time, because these criteria were listed as exclusionary criteria when you agreed to participate in the study. Participants that harass the RA or behave in an inappropriate and unprofessional manner with the RA will be withdrawn from the study. Participants with unstable Zoom connections may also be withdrawn from the study. Once again, compensation will be prorated ($10 for each 30 minutes) if you are withdrawn from the study for any reason.

You may withdraw from the study at any time without consequence by informing the research assistant that you would like to end the testing session. The research assistant may ask for the reason you are asking to withdrawal (to reduce the issue for future participants) but will honor your request and will cease the testing session. If you become distressed by your participation in this study, several resources are available to you. You may first contact Dr. Carrie Cuttler, carrie.cuttler@wsu.edu. If you feel it is necessary, you will also be provided with the phone numbers for crisis lines (e.g., Pullman 24-hour Crisis Line, Crisis Text Line), and can seek medical attention.

Will my information be kept private?

The data for this study will be kept confidential to the extent allowed by federal and state law. Under certain circumstances, information that identifies you may be released for internal and external reviews of this project. It is also possible that the data, particularly cognitive test results collected online using DRUID, could be breached or compromised.

A confidential ID code will be assigned to you when you agree to participate in this study. This ID code will be used to identify your data (survey data, cognitive test results, and other responses you provide) throughout the study. Your name and identifying information will be kept separate from the data you provide throughout the study, and will be stored on an encrypted, password protected computer to protect your information and confidentiality. Only the PI (Dr. Carrie Cuttler) and Co-I (Aria Petrucci) will have access to your personal contact information throughout the study. All of the researchers working on this project have signed a confidentiality agreement. All of your communications between yourself and all researchers working on this project will be kept private. Data will be stored in a locked file cabinet in a locked room and on an encrypted, password

protected computer at WSU. Carrie Cuttler, Amanda Stueber, and Aria Petrucci will have access to the data files. These datafiles will be stripped of identifying information including name and contact information, and a separate, password protected file which links ID codes to participant contact information will be stored on an encrypted computer. Only Carrie Cuttler and Aria Petrucci will have access to this file containing identifying information.

The results of this study may be published or presented at professional meetings, but the identities of all research participants will remain anonymous. Data containing personally identifiable information from this study will be kept for 3 years. Data not containing personally identifiable information will be kept indefinitely and may be made available to journal editors and reviewers or may be made publicly available online as some journals now require this as part of the publication process. All data will be kept confidential.

Are there any costs or payments for being in this study?

There will be no costs to you for taking part in this study. The CBG and placebo will be provided to you free of charge, but you will need to contact the distributor directly to obtain the materials (there will be no shipping costs) before your testing sessions. If you experience discomfort or injury and require medical care the associated medical costs will not be reimbursed. If you choose to continue to use the DRUID app and make in-app purchases you will not be reimbursed.

You will receive a $31 Amazon gift card for taking part in each 90-minute testing session. If you complete both sessions, you will receive a total of $62 in Amazon gift cards. If you decide to quit the study, or are withdrawn from the study, you will receive a prorated amount based on the amount of time you spent completing the study (e.g., $10 per 30 minutes in the form on an Amazon gift card).

Who can I talk to if I have questions?

If you have questions about this study or the information in this form or if you would like to discuss a research-related injury or discomfort, please contact the researcher Dr. Carrie Cuttler, Department of Psychology, Johnson Tower, Room 211, 509-335-0681, carrie.cuttler@wsu.edu. If you have questions about your rights as a research participant or would like to report a concern or complaint about this study, please contact the Washington State University Institutional Review Board at (509) 335-7646, or e-mail irb@wsu.edu, or regular mail at: Neill 427, PO Box 643143, Pullman, WA 99164-3143.

What if I have a study-related injury or want to withdraw?

If you have a study related injury, illness, distress and want to report this to the researchers, contact Dr. Carrie Cuttler, Department of Psychology, P.O. Box 644820,
Johnson Tower, Room 211, 99164-4820, 509-335-0681, carrie.cuttler@wsu.edu. In order to withdraw your previously collected data from the study you must provide your complete name and date of participation. There are no consequences for withdrawing your data from the research study.

What are my rights as a research study volunteer?

Your participation in this research study is completely voluntary. You may choose not to be a part of this study. There will be no penalty to you if you choose not to take part. You may choose not to answer specific questions or to stop participating at any time. The RA will email you a copy of the consent form for your records if you request a copy.

What does my signature on this consent form mean?

Your signature on this form means that:

- You understand the information given to you in this form
- You have been able to ask the researcher questions and state any concerns
- The researcher has responded to your questions and concerns
- You believe you understand the research study and the potential benefits and risks that are involved.
- You are giving your voluntary consent to take part in the study.

Date: [Enter date online]

Statement of Consent

Yes, I agree
No, I disagree