Protocol Title: The potential of kava in enabling tobacco cessation - its holistic effects in managing stress and insomnia associated with abstinence

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ABSTRACT

As the leading cause of numerous preventable diseases, smoking results in half a million premature deaths each year in the US and another 16 million American adults living with a serious illness. Indeed, about half of smokers will die of smoking-related problems if they do not quit. Most smokers are aware of such deleterious health effects and have the intention to quit. Tobacco cessation, however, is very challenging, partly due to abstinence-associated stress and insomnia. Current tobacco cessation medications are not designed to address these problems, which have contributed to their limited success in enabling tobacco cessation. There are currently about 34 million American adult smokers and the number is not expected to decrease significantly in the near future. Novel interventions are thus urgently needed that would resolve these challenges, which may significantly improve the success rate of tobacco cessation. On the basis of its traditional history and our preliminary data, kava is such a candidate. Kava is a traditional beverage consumed among the South Pacific Islanders for relaxation, stress reduction, and sleep improvement. It is also marketed as a dietary supplement in the US. Incorporating rigorous safety measures, we completed a pilot trial among active smokers with a one-week ingestion of a kava supplement. The results for the first time revealed kava's potential in enabling tobacco cessation with promising effects on a panel of biological signatures associated with tobacco use, stress, and sleep. The main goal of this R33 application is to replicate the effects of kava on the biological signatures of tobacco use, stress, and sleep in addition to its compliance and safety among smokers. We propose to perform a double-blind randomized placebo controlled two-arm trial among 76 smokers with intention to quit, who will consume AB-free kava at a dietary supplement dose or placebo, 3 times per day for 4 weeks with two follow-ups. Aim 1 will evaluate the compliance and safety of AB-free kava use among smokers and assess changes in smoking behaviors. Aim 2 will quantify a panel of non-invasive translatable biomarkers to objectively evaluate AB-free kava's holistic effects on biological signatures associated with tobacco use, stress, and sleep. We hypothesize that AB-free kava is a novel and promising intervention to facilitate tobacco cessation via its holistic effects in managing stress and insomnia associated with abstinence. If the results from this study support our hypothesis, kava could emerge as an affordable and accessible dietary supplement candidate for tobacco cessation.

1. SCIENTIFIC RATIONALE AND BACKGROUND:

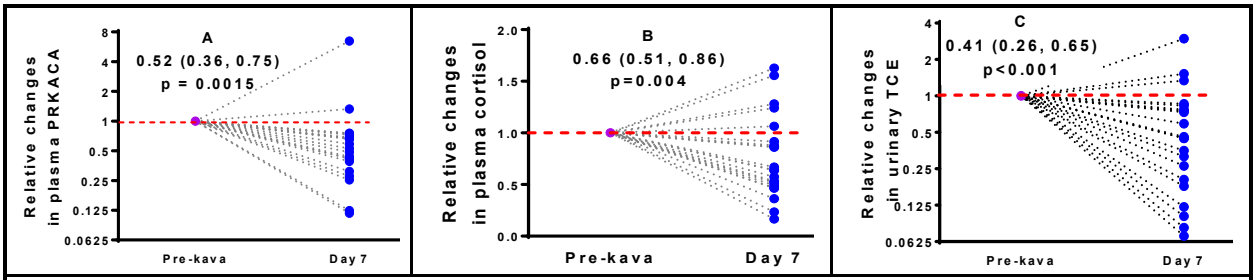


Fig. 1. Impact of one-week kava on urinary TNE (A), plasma PRKACA (B), plasma cortisol (C), and urinary TCE (D). Two-tailed paired t-test was performed (n = 21). A ratio of geometric means and 95% CI presented.

Currently, there are 34 million adult smokers in the US [1, 2] with little indication that this number will decrease significantly in the near future [3]. Tobacco use is the leading cause of numerous preventable diseases and about half smokers will die of smoking-related problems if they do not quit [1]. Given that ~ 70% of adult smokers want to stop smoking and over 50% of them make a quit attempt annually [4], this devastating health burden could be significantly reduced if the success rate of tobacco cessation can be improved. It was also observed that two thirds of those planning to quit were interested in trying complementary approaches to facilitating tobacco cessation [1], which is currently lacking. Effective complementary tobacco cessation interventions, therefore, need to be developed to support smokers achieve cessation and reduce the risk of associated diseases.

The first-line medications to facilitate tobacco cessation include nicotine replacement therapy, bupropion, and varenicline. These medications typically result in moderate success rates but suffer from significant relapses [5]. Some of them are also associated with various adverse side effects, which may contribute to their limited

success in tobacco cessation. One common side effect is trouble in sleeping [6]. It has been even proposed that adjunctive treatment targeting sleep disturbance may improve abstinence rates [6, 7].

Kava has a long history of safe use as a beverage to help people relax and improve sleep with daily dosages ranging between 750 – 8,000 mg kavalactones [8-12]. WHO and others have reviewed the reported kava safety data and concluded that kava's purported hepatotoxic risk is rare if any (< 0.3 case per one million daily doses) [13-21], particularly with the right cultivars and preparations [14]. Kava therefore has always been on the US market as a dietary supplement. Since traditional kava has been safely used for centuries and its daily kavalactone dose is significantly (3 – 100 times) higher than its anxiolytic and dietary supplement regimens (120 – 280 mg kavalactones daily) [8-12, 22], kava's hepatotoxic risk may be associated with ingredients enriched in the anxiolytic preparations. One possibility is the higher abundance of flavokavains A and B in the anxiolytic form (~100 times) than in traditional kava [23]. Flavokavains A and B are also much more abundant in low-quality kava cultivars than in noble kava cultivars [24]. They are the most cytotoxic compounds in kava [23, 25] and have induced hepatotoxicity in lab animals [26, 27]. These data suggest that flavokavains A and B likely account for kava's hepatotoxic risk.

A kava formula, free of flavokavain A and B and mimicking traditional kava preparation, has been developed by Thorne (namely AB-free kava). AB-free kava has rigorous Chemistry Manufacturing and Controls (CMC) documentation, high quality control and quality assurance, and an enabled IND status (142838) with an ongoing double-blind randomized placebo-controlled trial among patients with generalized anxiety disorder (NCT03843502) using the same regimen as proposed in this application. This formula has also demonstrated outstanding safety profiles in several animal models [28-31]. The pharmacokinetics of six major kavalactones in AB-free kava has been characterized among healthy participants [32], indicating that three times daily regimen offers better kavalactone exposure.

Based on its relaxing and sleep improvement activity [33-36], kava has the potential to facilitate tobacco cessation and could be potentially more effective. Its dietary supplement status may make it more acceptable to smokers as well [37]. These potential benefits were further supported by the results of our pilot kava trial among smokers ([38]) that one week of kava use reduced biomarkers on tobacco use, stress and increased biomarkers on sleep.

The main goal is to replicate the effects of kava on biological signatures of tobacco use, stress, and sleep in addition to its compliance and safety among smokers.

2. STUDY AIMS AND OBJECTIVES:

This study has two aims. Aim 1. To document AB-free kava compliance, identify potential issues and characterize its effects on smoking, stress, and sleep associated behaviors. Aim 2. To quantify a panel of non-invasive clinically translatable biomarkers to objectively evaluate AB-free kava's holistic effects on biological signatures associated with tobacco use, stress, and sleep.

HYPOTHESIS: We hypothesize that AB-free kava (a properly formulated kava) is a novel promising intervention to facilitate tobacco cessation via its holistic effects in managing stress and insomnia associated with abstinence. To test this hypothesis, we will perform a double-blind randomized placebo controlled two-arm trial among 76 smokers with intention to quit, who will consume AB-free kava at a dietary supplement dose or placebo, 3 times per day for 4 weeks with two follow-ups.

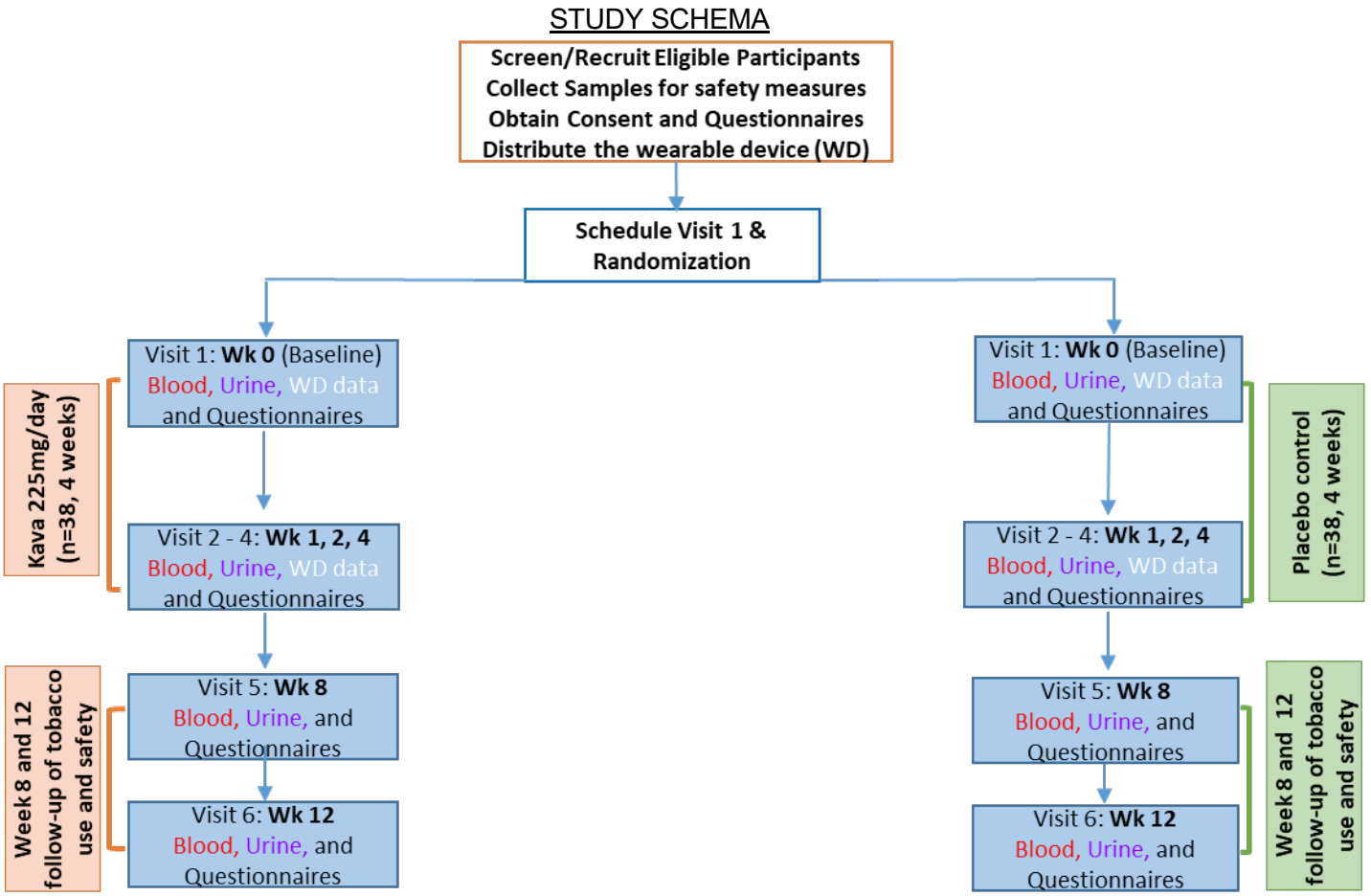
A. Primary Objective: To evaluate AB-free kava compliance and identify potential issues.

B. Secondary Objective(s): To examine whether AB-free kava has the potential to help facilitate tobacco cessation – tobacco cessation-related questionnaires and reduction in urinary TNE (total nicotine equivalents, which measures nicotine, cotinine, and 3-hydroxycotinine and their conjugates separately). To examine whether AB-free kava has the potential to reduce stress and improve sleep – standard questionnaires and associated biomarkers (plasma PRKACA, plasma cortisol, urinary TCE, and urinary NAS).

C. Exploratory Objective: To examine the sociocultural context to better understand factors that may play a role in participants' enrollment and willingness to engage in kava use as a dietary supplement in tobacco

cessation. To use a wrist wearable device to objectively monitor parameters related to sleep, which complement self-reported sleep measures.

3. STUDY SCHEMA AND/OR SCHEDULE OF EVENTS:



This is a double-blind randomized placebo-controlled intervention trial. Methods of the protocols have been established in the PI and Co-I's laboratories to adequately answer the questions addressed in the objectives. The trial will require resources from the UF Family Medicine Clinics and UF Consent2Share to help enroll active smokers with the intention to quit, who are otherwise healthy, to be randomized into the placebo and AB-free kava (225 mg dose) arms, being exposed for four weeks, with a total of six visits (Week 0, 1, 2, 4, 8 and 12) to evaluate the compliance and potential issues of AB-free kava use among the participant, explore the potential effect of the AB-free kava intervention on tobacco dependence, tobacco use, stress and sleep and associated biomarkers. Placebo or AB-free kava interventions are 4 weeks long with one capsule each time and three times daily approximately administered via oral at 8 AM, 1PM, and 6PM (total of 3 capsules daily). The dose of AB-free kava for 225 mg regimen will be 75 mg of kavalactones per capsule. There will be no dose modification and the use will discontinue if severe adverse effect is detected, which is detailed later.

Clinic Staff members from the UF Health Family Medicine Main Street Clinic and Spring Hill Clinic, under the supervision of Dr. Malaty and Dr. Orlando, will identify potential participants and briefly introduce the overall goal of the study, typically during the clinic visit. Once a potential participant is identified, the clinic staff member will refer the candidate to the study coordinator. The study coordinator will conduct a pre-screening interview to explain the study, its potential benefits/risks, and determine the eligibility. Those meeting primary inclusion/exclusion criteria and interested in participation will be scheduled for an in-person assessment. At the assessment visit, participants will be informed and will verbalize understanding that consent is voluntary and that they have the right to withdraw from the study at any time they wish without any consequences to any health care they are receiving currently or in the future. After having their questions answered, if they would like to participate in the study, they will agree to refrain from engaging in any other smoking cessation while

participating in this study and sign an informed consent form. Participants are informed that they will receive a $50 gift card at each Visit 1 – 6 that will total to $300 if they attend all visits. This $300 amount does not include the optional $25 that select subjects may receive for consenting to do the Post-Treatment interview at Visit 4 (or whenever they stop treatment). The post-treatment interview is not required and will not create a deviation if missed. If subject's attend all visits and do the optional Post-Treatment interview, then they can receive a total of $325.

Once a participant signs the consent form electronically in REDCap, s/he will perform a breath CO test to evaluate smoking status. Blood will be screened for ALT, AST, ALP, and total bilirubin. Pregnancy test for females of childbearing potential will be done with a spot urine. Upon confirming tobacco use, normal liver function, and other criteria, qualified participants will be enrolled into this study, set up Visit 1 (typically within one week), and randomized into one of the two study arms. A GT3X+ accelerometer wearable device will be provided to the participant and will be worn for four days before the first four visits at Week 0, 1, 2, and 4. The wearable device will use a micro-electro-mechanical system (MEMS) based accelerometer and an ambient light sensor to measure physical activity and sleep. The Research coordinator will provide instruction of the use of the wearable device and provide demonstration.

Visits 1 – 6: During each of the following visits (each should take about 30-60 minutes), participants will be screened for ALT, AST, ALP, total bilirubin, breath CO test, and questionnaires administered. An additional blood sample (10 mL, onsite) and 24-h urine (Participants will be provided the collection container during each visit and will bring their urine samples to their next visit) will be used for biomarker assays. The participant then will be provided with medications and written instruction of use, supplies for the next 24-h urine collection, and scheduled for the next visit. During Visit 1 – 4, the data in the GT3X+ wearable device will be collected by study coordinator at each visit. At Visit 4, the GT3X+ wearable device will be collected from the participant.

The questionnaires include:

- Self-Reported Measure of Smoking: documenting the number of cigarettes smoked in the past 7 days.
- Fagerström Test for Nicotine Dependence (FTND): a 6-item scale measuring the level of nicotine dependency or addiction. It assesses how soon tobacco use begins each day, which cigarettes during the day a person could do without, how smokers cope in places where they cannot smoke, and how frequently and how deeply they smoke.
- Modified Cigarette Evaluation Questionnaire (mCEQ): a 12-item scale, rating several dimensions (satisfaction, psychological reward, nausea or dizziness, craving relief; enjoyment of airway sensations). It assesses the degree to which participants experience the reinforcing effect of smoking.
- Brief Questionnaire on Smoking Urges (QSU-Brief): a 10-item scale, assessing the features of craving, including the anticipation of relief of nicotine withdrawal, anticipation of positive outcomes of smoking, desire to smoke, and intention to smoke.
- Perceived Stress Scale (PSS): a 10-item scale measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. The scale also includes a number of direct queries about current levels of experienced stress.
- Insomnia Severity Scale: a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. Dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Because of kava's potential benefit to sleep, this questionnaire will generate preliminary data about kava's mechanism in facilitating tobacco cessation.
- Modified Pittsburgh Sleep Quality Index (MPSQI): contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available), which has been widely used to evaluate tobacco-induced sleep disturbances.
- Modified Ask Suicide-Screening Questions (MASQ): consists of four yes/no questions to identify individuals that require further mental health/suicide safety assessment. According to FDA recommendation for any interventions with neurological activities, the original ASQ is used to assess suicide risk because of its peer-reviewed effectiveness and the lower burden on the participants. This study has modified the questions to be less intrusive into participants mental health history beyond what's needed for eligibility confirmation.

- NIH Sleep Diary: consists of 12 self-reported criteria to record the quality and quantity of sleep; use of medicines, alcohol, and caffeinated drinks; and how sleepy subject feels during the day. This questionnaire is optional and failure to complete it will not result in a deviation.

At the end of the study (Week 12) or when a participant drops out of the study, an exit interview will be performed with open-ended questions to obtain feedback about the trial from the participants.

At the end of study treatment, Week 4, or at the time the participant withdraws from this study, subjects will be offered an opportunity to participate in a post-treatment interview, which is not required. The post-treatment interview will no longer be collected after 25 participants have completed it. If they choose to participate they will receive an additional $25 to the $50 they are already being given for their attendance. Participants will be purposively sought to ensure comparable subgroups of racial and ethnic minorities and white participants. By recruiting subgroups, we can explore cultural similarities and differences in their experiences. We expect to recruit 25 participants to ensure thematic saturation. However, data collection and analysis will be concurrent to ensure saturation is reached. This interview will help to identify facilitators and barriers to trial enrollment and retention.

In-depth, semi-structured interviews will be conducted via phone or Zoom by the research coordinator, given their established rapport and trust [39]. Fisher (co-I), a qualitative methodology expert in health behavior intervention development, will provide oversight on data collection and analysis. She will also develop the semi-structured script and train the coordinator on in-depth interviewing. Interview questions will explore participants' experiences with kava to identify critical factors to promoting future trial enrollment, adherence, and sustained healthy behavior change [40, 41]. Questions will explore facilitators and barriers to enrollment and retention as well as sociocultural factors informing participants' health behavior and ongoing willingness to engage in kava use. These include exploring the influential role of cultural norms or beliefs, experiences within their family system, and prior use or beliefs about kava. The interviews need to be audio recorded so that they can be professionally transcribed. The transcriptions of interviews are the qualitative data that are then thematically analyzed by a qualitative research scientist. Without audio files or transcriptions, there is no reliable data. This is standard and best practices in qualitative methodology.

Data will be managed using a data management software program (ATLAS.ti). A thematic analysis will be conducted by a qualitative analyst trained by Fisher, who will oversee analysis and codebook development [42, 43]. To maintain sensitivity to cultural differences, data will be segmented by race and ethnicity and analyzed by group to triangulate findings. An additional coder will be used to validate the final codebook to further promote rigor in analysis [44]. Audio recordings will begin after consent has been obtained and captured using a digital recording device. Audio files (mp3) will be downloaded immediately after the interview onto a secure UF computer. Files will be uploaded for professional transcription with a vendor that has been approved by UF risk management with associated approved procedures. Files will be saved as a code instead of patient names. This code will be used on transcriptions as well. Only the PIs and relevant study personnel (e.g., Co-I overseeing the qualitative analysis) will have access to the code-identifier file, which will be stored in on a UF computer. All transcriptions (i.e., data) will be de-identified prior to thematic analysis to ensure confidentiality of participants. No identifying information will be used in any publications or presentations to protect the confidentiality of participants. Audio files will be destroyed once analysis has been completed. Transcripts will be destroyed once all analyses are completed or within two years once the study period has ended.

Data and biological sample collection and storage All data (participant information, questionnaire responses, values of biological samples and others) will be stored in a REDCap database. REDCap is a HIPAA-compliant, highly-secure, and intuitive-to-use web-based application designed to capture and store data for clinical research, including questionnaire data from research participants. Data will be exported into a SAS data set for analysis. Data integrity will be evaluated using descriptive statistics (e.g., means, standard deviations, frequencies, percent, range) appropriate for measurement levels. Checks for implausible or out-of-range values, distributional forms, and missingness will be performed.

For biological samples, a research assistant will retrieve the urine and blood samples from the Clinic within 1 hour after the participant's visit and deliver to the Xing lab. The total volume of the urine sample will be recorded to the closest 10 mL. The urine samples, upon mixing well, will be split into 10 x 1 mL, 5 x 15 mL, 2 x 100 mL

and stored at – 80ºC. The blood samples will be processed into plasma, buffy coat and red blood cells and stored at – 80ºC. Detailed information of these samples, including participant ID, visit #, sample information, and missed dosing or sample(s), will be recorded in the REDCap database.

4. STUDY DESIGN

To rigorously test our hypothesis and build the solid foundation for future AB-free kava translation among addicted smokers to facilitate tobacco cessation, we propose a double-blind randomized placebo-controlled longitudinal trial (4-week AB-free kava intervention vs. placebo with two follow-ups). Briefly, addicted smokers with INTENTION to quit will be enrolled and randomized into two groups (those NOT willing to quit will be referred to Tobacco Free Florida, the state tobacco cessation program, or other tobacco cessation studies). One group will take placebo capsules and the other group will take AB-free kava capsules (one capsule each time, 3 times daily, each capsule is 75 mg kavalactone) for four weeks. Safety monitoring and sample collections will be implemented at Week 0, 1, 2, 4, 8 and 12 respectively. Two follow-ups (Week 8 and 12) are designed to 1) explore the sustainable potential of AB-free kava; and 2) capture delayed adverse effects if any, both of which are critical for participants and future development. AB-free kava regimen proposed herein remains the same as in the pilot trial [38], supported by our recent pharmacokinetic results (the half-lives of the main ingredients in AB-free kava are no more than 3 hours). The 4-week AB-free kava exposure is expected to provide sufficient data about AB-free kava's compliance, efficacy and safety while minimizing potential risks among the participants. At the end of Week 12, all enrolled participants will be recommended to Tobacco Free Florida to maximize the chance of tobacco cessation.

National Institute of Health (NIH) is considering to fund the proposed clinical trial via a 3-year clinical trial grant through the R33 mechanism from National Center for Complementary and Integrative Health (NCCIH). The methods, protocols, and expertise are all in place in the PI and Co-I's research group. The proposed objectives are expected to be achievable in the 3-year funding period. The safety of the participants will be closely monitored that the intervention will stop following the rules below:

1. Participants will be assessed for ALT, AST, ALP and total bilirubin using blood samples collected during the visits at baseline, week 1, 2, 4, 8 and 12 to monitor potential acute or delayed hepatotoxic risk. During the visits at baseline, week 1, and 2, the participant will receive the drug supplies for 1 week (at baseline), 1 week (at week 1), and 2 weeks (at week 2). The ALT, AST, ALP and total bilirubin test results will be available to the research coordinator within 24 hours after the blood sample collection and the participant will be notified of the results immediately after they become available if the levels are out of the range as defined below. The patient will be instructed to stop taking the study drug if they are not in contact with the clinic regarding their lab results within 24 hours of the blood draw. During the period of time between blood sampling and lab results, which is within 24 hours, the participant will continue to take the medication as scheduled. This is the standard protocol for the clinical evaluation of standard therapeutics, even those with high risk of hepatotoxicity. Given the very low risk of hepatotoxicity reported for kava (< 0.3 case per 1,000,000 dosages), the protocol has built in adequate measures to minimize the potential risk associated with kava use without significantly compromising the goal of the trial. Participants, whose ALT, AST, ALP or total bilirubin increases > 3 x the upper limit of normal (ULN) but ≤ 5 x ULN, will retest after 48 to 72 hours. The patient will continue taking the study drug during this time. If ALT, AST, ALP or total bilirubin increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, study drug will be discontinued and participant referred for further clinical evaluation.

2. When 25% participants complete all study visits (Visit 0-6), safety data of all participants will be analyzed by Data Integrity and Safety Committee (DISC) independently to determine whether AB-free kava intervention has any potential risk. The same practice will be implemented at 50% and 75% completion.

5. SELECTION OF SUBJECTS

Justification for UF Health Family Medicine Main Street Clinic and Spring Hill site a) Over 1700 adult smokers visited the Main Street Clinic last year for annual checkup, >50% of whom smoke at least 10 cigarette/day. Although our exclusion criteria is stringent (detailed below), we expect at least 15 – 20% recruitment rate given the high success to recruit participants in family clinics for tobacco trials; b) successful track record of recruiting smokers to support clinical research, including collaborations between Drs. Salloum and Malaty (co-Is), who have previously

recruited 120 adult smokers from the same clinic in 4.5 months (NCT03836573); c) electronic health record information of patients in the clinics will help identify eligible participants – those without previous liver diseases; and d) most importantly, the clinical expertise, resources, and facilities will minimize potential adverse effects in this trial. The Spring Hill site has a similar patient population and clinical research structure. We propose two sites to maximize the enrollments.

There are no additional requirements with respect to gender, employment, geographical, language, or other factors.

Our targeted accrual goal is 76 active smokers. Based on our previous enrolling experience at the Family Clinic and our rather stringent inclusion/exclusion criteria, the enrollment is expected to be 1.5 – 2.5 years with the duration of each participant to be around 12 weeks.

The participants will be referred to study team via a UF Health Family Medicine Main Street Clinic and Spring Hill sites. Specifically, clinic staff members from the clinic under the supervision of Dr. John Malaty and Dr. Frank Orlando will identify potential participants and briefly explain the study. Once a potential participant is identified, the clinic staff will refer the candidate to the study coordinator. Participants will also be referred to the study team through the UF Consent2Share program.

Justification for excluding pregnant women. Given the proposed mechanism of AB-free kava to facilitate the reduction of tobacco use through the modulation of stress, pregnant women will be excluded from this study because pregnancy is expected to introduce significant changes on mental status and hormone physiology. Such variations are expected to compromise the sample size justification and therefore the primary goal of this early-phase clinical study.

Total Number of Subjects (should be total of a + b): **76**
Total Number of Subjects (affiliate sites, if applicable): **not applicable**
Total Number of Subjects (UF site): **76**

Key Inclusion Criteria:

A) adults aged 21 years or above (legal age for smoking in the U.S.) and 75: there is no knowledge that kava's pharmacology could be age dependent; the upper age of 75 is defined to minimize the risk for elderly;
B) self-reported smoking at least 10 cigarette/day for the past year with INTENTION to quit;
C) expired carbon monoxide level of more than 8 ppm at recruitment;
D) willingness to participate in the proposed study;
E) access to a functional telephone;
F) expected presence in the study's geographical area for the next 4 months;
G) not currently enrolled in any smoking cessation programs; and
H) for female subjects of childbearing potential will be required to practice acceptable methods of birth control (the acceptable methods of birth control include birth control pills, Birth Control Shot, Birth Control Implant, IUD, Diaphragm, and cervical cap).
I) if a participant takes kava dietary supplement, a 2-week washout period is needed for the participant to initiate this study or if a participant participated in a kava trial before, such as the kava JEK trial, the participant could be enrolled if the inclusion criteria above are met, including the 2-week washout period.

Key Exclusion Criteria <u>(any of the following)</u>:

A) diagnosed with cancer (other than non-melanoma skin cancer);
B) diagnosed with liver dysfunction or with previous liver diseases;
C) levels of ALT, AST, ALP or total bilirubin over limit of normal (ULN) range at prescreen;
D) inability to refrain from acetaminophen, alcohol (no more than one drink daily via self-report), or other potentially hepatotoxic substances;
E) use any other non-cigarette nicotine containing products such as smokeless tobacco, cigar or e-cigarettes; or
F) are pregnant or nursing (lactating) or of childbearing age planning to become pregnant or unwilling to use adequate contraception during the study;
G) participant answered "Yes" to any of the MASQ questions 1 through 4, or refuses to answer. If subject answers 'Yes' to question 4 but the most recent suicide attempt took place >12 months from screening visit then subject is still eligible.

6. STUDY PROCEDURES

Enrollment and study procedures Permission to conduct this study will be obtained from the UF IRB prior to start. Clinic Staff members from the UF Family Clinic will identify potential participants and briefly explain the study. Once a potential participant is identified, Clinic Staff members will refer the candidate to the study coordinator. The study coordinator will conduct a pre-screening interview to determine the eligibility. Those meeting primary inclusion/exclusion criteria and interested in participation will be scheduled for an in-person assessment. At the assessment visit, participants will be informed and will verbalize understanding that consent is voluntary and that they have the right to withdraw from the study at any time they wish without any consequences to any health care they are receiving currently or in the future. After having their questions answered, if they would like to participate in the study, they will agree to refrain from engaging in any other smoking cessation while participating in this study and sign an informed consent form.

Once a participant signs the consent form electronically in REDCap, the participant will complete breath CO test to evaluate smoking status. Screening procedures performed per Standard of Care within the screening window can be used even if prior to consent. Upon confirming tobacco use, normal liver function, no alcohol abuse (via self-report and questionnaires), qualified participants will set up Visit 1 (typically within one week), and be randomized into one of the two study arms. During each of the following visits, participant liver function will continue to be monitored with blood tests, a breath CO test, and questionnaires. An additional blood sample (10 mL) and 24-h urine (collected the day before the visit, patients will be provided collection container during each visit) will be used for biomarker assays. The participant then will be provided with medications, written instruction of use, and supplies for the next 24-h urine collection, and scheduled for the next visit. The questionnaires to be administered have been previously listed in the Study Schema and/or Schedule of events section.

Randomization Participants who meet eligibility criteria will be randomized to the AB-free kava (225) or the placebo group using a 1:1 allocation scheme, stratified by age, gender and heavy/light consumption of cigarettes per day. IDS randomizes the subject based on the criteria entered with the first Order placed in EPIC for Study IP. IDS does not provide any documentation to the study team that randomization occurred. Upon completion of all proposed analyses, IDS will provide the randomization record to the PI, Co-Is and Dr. Huo to un-blind assignment. As IDS will operate independently of the study team, the study will be a double-blind trial.

Intervention AB-free kava (225) and placebo will be obtained from Thorne Research Inc. Chemistry, Manufacturing and Controls (CMC) data have been reviewed by Food and Drug Administration (FDA) with an enabled Investigational New Drug (IND, #142838) for a trial among patients with generalized anxiety disorder (GAD). The IND for a similar study among smokers with NO intention to quit has been approved (IND #157256) and this study will be added as an amendment. Such AB-free kava capsules have been analyzed in-house as well for its abundance of kavalactones and lack of flavokavains A and B by our established LC-MS/MS method [45]. AB-free kava or placebo will be administered as follows: one capsule by mouth ideally with meals three times a day (around 8:00 a.m., 1:00 p.m., and 6:00 p.m.) for 28 days. This will result in a daily dose of 225 mg kavalactones for AB-free kava group participants. If a dose is missed, participant will not double the dose at the next scheduled time but document the missed dose and return the missed dose at the next visit.

Retention strategies and incentives The study team has an excellent history of retaining clinical trial participants. We will always use respectful, empathetic communication and be considerate of participants' time when scheduling research activities. Compliance and retention will be maximized via the following methods: a) close monitoring during participation; b) a reminder phone call to confirm study visits; c) 24/7 access to the study team during participation; and d) establishing appropriate rapport such that the participant feels motivated to return. Participant will also receive a gift card for each visit as compensation. These strategies should minimize missing data and improve data validity.

Preparing, dispensing and recording study supplements by IDS Supplies for each participant will be prepared by IDS following randomization. Instructions on use and storage will be provided in writing. Participants will be asked to keep track of missed dose. Unused materials will be returned at the next visit, recorded and destroyed by IDS. IDS will maintain a Study Drug Accountability log for each participant, which will record participant ID, randomization code, medication ID, dates of medication dispensed, returned, missed dose, number of capsules returned, and medication destruction.

Data and biological sample collection and storage All data (participant information, questionnaire responses, values of biological samples and others) will be stored in a REDCap database. REDCap is a HIPAA-compliant, highly-secure, and intuitive-to-use web-based application designed to capture and store data for clinical research, including questionnaire data from research participants. Data will be exported into a SAS data set for analysis. Data integrity will be evaluated using descriptive statistics (e.g., means, standard deviations, frequencies, percent, range) appropriate for measurement levels. Checks for implausible or out-of-range values, distributional forms, and missingness will be performed.

For biological samples, a research assistant will retrieve the urine and blood samples from the Clinic within 1 hour after the participant's visit and deliver to the Xing lab. The total volume of the urine sample will be recorded to the closest 10 mL. The urine samples will be split into different aliquots and stored at – 80ºC. The blood samples will be processed into plasma, buffy coat and red blood cells and stored at – 80ºC. Detailed information of these samples, including participant ID, visit #, sample information, and missed dosing or sample(s), will be recorded in the REDCap database.

Minimizing potential risk to confidentiality: Any concerns related to the intervention and privacy will be shared with the PI and every effort will be made to protect the participants' information during the study. All study personnel are accustomed to maintaining and ensuring patient confidentiality in the course of their work. In addition, all study personnel are highly trained in research procedures and in issues regarding protection of participants' rights and privacy. All members of the research team, including the PI, coinvestigators, study coordinator, data collectors, research assistants, data manager, and all students associated with the project will complete UF-mandated human subject training prior to study commencement. Participants' identities will be protected through the following measures: consent forms will be stored behind a locked door and in a locked filing cabinet accessible only by the PI, and all identifying information will be stored in a separate, secured location from data that is collected during the study. Access to locked files will be restricted to essential personnel only. In addition to consent and identification files that are secured, all data files will be coded in a manner that makes identification of the participants extremely unlikely. Indeed, participants will be given a numerical ID code to ensure that inadvertent or unauthorized identification does not occur. Data will receive additional layers of security because the whole building, floor, and office in which locked records are maintained have restricted, keyed access. The anonymous codes assigned to participants will be verified and maintained by Dr. Salloum throughout the study, and codes with names will be provided only to meet federal guidelines applicable to the facility. Data will be entered into a REDCap database developed for the project. REDCap (Research Electronic Data Capture) is a secure, HIPAA-aligned web-based application designed to support traditional case report form data capture. REDCap's automated export procedure will be utilized to export data into a SAS data set for analysis. Our research coordinator will conduct the screening of potential participants working closely with the clinical staff. The research coordinator will meet with Dr. Salloum weekly to discuss study progress.

Environment Assessment (EA): An Environmental Assessment is not required because the action requested qualifies for a categorical exclusion per 21 CFR 25.31(e). To the applicant's knowledge, no extraordinary circumstances exist per 21 CFR 25.15(d).

7. POSSIBLE DISCOMFORTS AND RISKS

Possible discomforts and risks from taking kava supplement are minimal. Preliminary data from a previous human study did not report any adverse events due to the consumption of kava supplementation. Because there is a potential for kava to affect the function of the liver through drug-herb interactions (<0.3 cases per million dosages), we will exclude any subjects with liver conditions and will monitor liver function during and after participants are receiving the intervention. AB-free kava (a kava preparation free of flavokavains A and B, the potential hepatotoxic ingredients in kava [26]) will be used the study as well, which is expected to have an improved safety profile. In the event that serum liver enzymes become elevated (3 times the normal range, which is considered as mild elevation clinically), participants will be notified immediately and retested in the next 48 – 72 hours. If increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. No severe adverse effects have been detected in the pilot kava trial and the recent GAD trial. Subjects have the potential to experience other side effects like digestive upset, headache, and dizziness. There is minimal risk associated with blood draws, which will be performed by certified professionals. Similarly, there are potential risks to confidentiality for participants in this study. However, these risks are minimal

given our procedures to protect against these risks. No other discomforts and risks (psychological, social, and/or economic), study participants are expected to encounter.

Given kava's potential neurological functions, we have built in a Modified Ask Suicide-Screening Questions (MASQ) form to assess the suicide risk. This questionnaire will be evaluated in real time by a trained study coordinator and can refer the patient to mental services if needed. Should such an emergency arise (statement or demonstration of active suicidal ideation), standard of care clinic procedures will be followed. Specifically, Alachua County Crisis Center would be called (352-264-6789) to have the patient evaluated in clinic (they send a staff member to clinic to see the patient) or the patient would be sent directly to a psychiatric facility (Vista or Meridian) for further evaluation and management either voluntarily or under a Baker Act. Additionally, all patients will be provided with resources for mental health help. The following numbers will be provided to patients in the ICF as well as upon request, UF psychiatry clinical sites (352) 265-4357., the Alachua County Crisis Center (352) 264-6789, and the Suicide and Crisis Lifeline 988 number. Kava use may result in sedation that the participant should not operate heavy instruments and should drive with care within 2 h after AB-free kava use, until they know how it affects them although such a risk is extremely low at the proposed dosage regimen. Additionally, collection of relevant medical history should be obtained at screening. Relevant is defined as any diagnosis of depression.

There are no potential financial risks that study participants may incur given the trial is free of charge to participants with all supplies provided and incentives are provided as well. Additionally, our clinical team has ample experience to protect against or minimize potential unexpected discomforts and risks.

8. POSSIBLE BENEFITS

There are several potential benefits from the study. AB-free kava may provide individuals randomized to the AB-free kava group a decrease in the urge to smoke, thereby making it an effective smoking cessation treatment. It may also improve the quality of sleep and reduce stress. This could be an effective, low-cost strategy to help people quit smoking and improve the quality of life. The risks for this study, as discussed above, are minimal and are far outweighed by the potential benefits to be gained regarding smoking cessation and the improvement in quality of life.

Regardless of the findings, this study will make a significant contribution to the literature in the field of supportive care. Indeed, it will fill a vital gap in the literature regarding the ability of kava to reduce the urge to smoke as well as reduce stress and improve sleep. In addition, this study will provide data for manuscripts that can be published in peer-reviewed, high impact journals, as well as manuscripts that can be published in lay journals for the public. Finally, this study will yield information that the investigators will disseminate at local, regional, state, and national meetings and will serve as the basis for conducting a follow-up, Phase III randomized control trial. In all presentations, we will use necessary scientific language about inclusion/exclusion criteria of the trial and about potential interaction with other widely used medications (i.e., acetaminophen) to minimize the risk of abuse.

9. ADVERSE EVENTS/UNANTICIPATED PROBLEMS

To minimize and closely monitor any potential Adverse Events/Unanticipated Problems, we will exclude individuals with elevated risk for hepatotoxicity, provide additional education, and closely monitor liver functions during the treatment period with 4 and 8-week follow-ups, which will be sufficient even based on kava's reported hepatotoxic cases [46]. Specifically, participants will be asked to control alcohol use and refrain from products containing acetaminophen through the study period. They will be provided with a reference list of medications that contain acetaminophen. ALT, AST, ALP, and total bilirubin will be assessed at every visit to ensure any adverse effects/risks identified and addressed. Alcohol use will be assessed via questionnaires (self-report). The AE collection period will start at Visit 1 when the first pills are received and end at Week 12. In addition to all serious adverse events (grade III and above), only non-serious adverse events (less than grade III) that are possible, probable, or definitely related will be reported into the study REDCap. Dr. Malaty or Dr. Orlando will supervise liver screening and safety monitoring. Participants with an increase in liver biochemistry will be referred to clinical services at UF for further evaluation to minimize the risk with plan detailed below. Dr. Malaty or Dr. Orlando, in consultation with Dr. Firpi (co-I and a hepatologist with clinical expertise in liver safety monitoring), will report any relevant adverse events to the Institutional Review Board (IRB) that meet the boards reporting requirements.

10. STATISTICAL ANALYSIS PLAN

Sample size determination: The sample size was estimated based on our primary biological signature endpoint data (TNE and PRKACA) from our pilot results. Using the pilot result of TNE as an example, the ratio of geometric mean of TNE after one week kava treatment is 0.68 with a standard error of 0.06. By assuming the placebo group exhibits 15% of the treatment effect, which is a consensus estimate in the literature [47, 48], and the same standard error as in the kava treatment group, the standardized effect size (Cohen's d) is d=1.01. Similarly, the Cohen's d for PRKACA is 0.89. Since in our proposed study, we will repeatedly measure these biomarkers of the same participant, we further assume the same Kava effect from week one through week four. By (i) varying within-participant correlation rho = 0, 0.2, 0.4, 0.6, and 0.8; (ii) at Bonferroni-corrected alpha level 2.5%(5%/2), and (iii) using a linear mixed model, 60 participants (30 per group) are needed to have at least 90% power for both TNE and PRKACA. By further assuming an 80% retention rate, which is the rate in similar studies [49], we plan to recruit 76 participants (38 per group).

Data analysis plan:

Principle All data (questionnaires and biomarkers) will be checked for out-of-range values and normality. Decisions regarding parametric vs nonparametric statistics and data transformation will be based on such results. Participants who received at least one dose of AB-free kava treatment or placebo, and have at least one more visit beyond the baseline visit will be considered as evaluable.

Missing data consideration We expect to have three scenarios for participants with respect to missing data. (1) Participants complete all visits and have no missing outcomes. They will be included in the statistical analysis. (2) Some participants may not complete all visits, but have outcomes for at least one visit after the baseline visit. These participants will be included in the statistical analysis as well. The missing outcomes will be handled by either the Last Observation Carry Forward (LOCF) technique or linear mixed model for longitudinal data analysis (see below for details). (3) Participants do not complete the first two visits after randomization. They will be excluded from data analysis and we will replace these participants (also see replacement plan section). An enrolled participant will be replaced if s/he (i) is not involved in the baseline visit, or (ii) is only involved in the baseline visit not in any of the next five visits. Such cases are expected to be no more than 20%.

Account for spurious data: All data (questionnaires and biomarkers) will be checked for out-of-range values and normality. If any spurious data (outliers) were identified, we will fit nonparametric statistical models to assess the robustness of our primary parametric data analysis.

Replacement Plan If a participant for any reason leaves the study, the study team will recruit a new participant to replace the study subject that is no longer in the study.

Primary Endpoint – Compliance Such information is critical for data interpretation and future clinical trial improvement. We will evaluate trial compliance in three ways as we have done in the pilot trial [38]: **i**) self-report of missed doses from participant diary; **ii**) returned pill counts by IDS pharmacy; and **iii**) urinary detection of dihydromethysticin (DHM) in participants during AB-free kava exposure since DHM is kava-specific [45]. In combination with the exit interview, the results will provide knowledge of the feasibility of AB-free kava use and potential issues among smokers with current treatment regimen.

Endpoints for Tobacco Cessation, Stress Reduction and Sleep Improvement – tobacco dependence (questionnaires), tobacco use (urinary TNE, total nicotine equivalents), stress (questionnaires), stress biomarkers (plasma PRKACA, plasma cortisol and urinary TCE, total cortisol equivalents), sleep (questionnaires and Fitbit measures), and sleep biomarkers (urinary 6-hydroxymelatonin and urinary N-acetyl serotonin, NAS).

Longitudinal data analysis To study the relationship between longitudinal outcomes and treatment effect, we will fit linear mixed effects models with subject specific random effects to account for within subject correlation, using R software lmer package. Linear mixed model can accommodate missing outcomes if they are missing at random. *Baseline outcomes and covariates including age, sex, race, smoking status will be adjusted to account for confounding effects.* Urinary TNE, one key endpoint, will be used to describe how the statistical models test our working hypotheses. The other measurements will follow the same model.

Hypothesis 1: active kava treatment (week 0 – week 4) is effective in reducing TNE as compared to the placebo group. To test this hypothesis, we will fit the following linear mixed model:

$$y_{it} = \mu + \alpha_i + \beta z_i t + \sum_{l=0}^{L} \gamma_l x_{il} + \varepsilon_{it}, \alpha_i \sim N(0, \sigma_0^2), \varepsilon_{it} \sim N(0, \sigma^2) \quad (1)$$

where y_{it} is the outcome variable (e.g., TNE) for subject i and week t ($0 \le t \le 4$ weeks); μ is the intercept term; $\alpha_i \sim N(0, \sigma_0^2)$ is the random effect with variance term σ_0^2 for subject i; z_i is the treatment indicator for subject i with $z_i = 0$ for the placebo group, and $z_i = 1$ for the kava group; β is the slope (TNE change per unit dose of kava per week) of the treatment effect compare to the placebo group; x_{il} is the l^{th} covariates for subject i with $l = 0$ for baseline level of the outcome measurements (e.g. baseline TNE) and $l = 1,2, \dots, L$ for L covariates (e.g., age, sex, race, smoking history, etc); $\varepsilon_{ik} \sim N(0, \sigma^2)$ is the error term with variance σ^2. In Equation (1), we will perform the statistical hypothesis testing (H_0: $\beta = 0$) to provide its p-value, point estimate and confidence interval. A significant p-value will indicate that the kava treatment significantly reduces TNE during week 0 through week 4 compared to the placebo group.

If we observe that the trajectory of kava's effect through weeks 0, 1, 2, and 4 is not linear, we will only consider observations at week 0 and week 4 to test **Hypothesis 1,** employ linear regression models.

Exploratory hypothesis 2: kava has a sustainable effect in reducing TNE in week 4 – week 12. We will test whether the kava effect (week 0 – week 4) can be extended to the follow-up period week 4 – week 12, when kava treatment is absent. The following two sub-hypotheses will be examined:

2a: kava's effect will sustain to the follow-up period. To test this hypothesis, we will only consider the kava treatment arm with $4 \le t \le 12$ weeks. We will fit the following linear mixed model:

$$y_{it} = \mu + \alpha_i + \beta_1 \mathbb{I}(t = 8) + \beta_2 \mathbb{I}(t = 12) + \sum_{l=0}^{L} \gamma_l x_{il} + \varepsilon_{it}, \alpha_i \sim N(0, \sigma_0^2), \varepsilon_{it} \sim N(0, \sigma^2) \quad (3)$$

where μ is the kava treatment effect at week 4; β_1 is the kava treatment effect at week 8 compared to week 4; β_2 is the kava treatment effect at week 12 compared to week 4; the rest of the parameters have the same interpretation as Equation (1). In Equation (3), we will perform the statistical hypothesis testing (H_0: $\beta_1 \le 0$ vs H_A: $\beta_1 > 0$, and H_0: $\beta_2 \le 0$ vs H_A: $\beta_2 > 0$). Rejecting the null hypothesis will imply $\beta_1 > 0$ or $\beta_2 > 0$, which indicates that the kava effect is not sustainable. In other words, TNE level will go up and the participants are likely to relapse. Failing to reject the null hypothesis will imply that the TNE level stays steady and the kava treatment effect likely sustains through week 8 and week 12. We will provide their p-value, point estimates and confidence intervals.

2b: the extended kava effect is superior to placebo. To evaluate this hypothesis, we will directly apply Equation (1) in **Hypothesis 1**, but treat week 4 as baseline, and week 12 as follow-up. Under this scenario, β is the slope of the extended kava effect (week 4 – 12) compared to the placebo group. We will perform the statistical hypothesis testing (H_0: $\beta = 0$) to provide its p-value, point estimate and confidence interval. A significant p-value will indicate that the extended kava effect significantly reduces TNE during the follow-up period (week 4 through week 12) compared to the placebo group, indicating kava's sustainable effect.

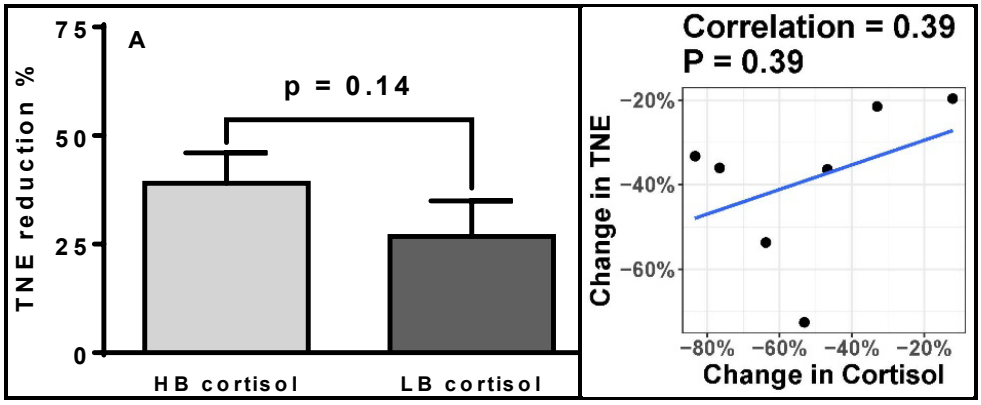


Fig. 2. Reduction of TNE among high baseline (HB) and low baseline (LB) TCE subgroups via one-tailed t-test (A) and correlation of TNE reduction and plasma cortisol reduction among HB cortisol subgroup (B).

Exploratory hypothesis 3: tobacco reduction by AB-free kava is potentially mediated via reductions in plasma PRKACA, cortisol, urinary TCE, NAS or 6-hydroxymelatonin. Our pilot data suggested that smokers with higher baseline levels of cortisol appeared to have more reductions in TNE upon AB-free kava use (Fig. 2A) while the extents of reduction in TNE correlate positively with the reductions in plasma cortisol (Fig. 2B). Although the difference and correlation were not statistically significant, these results support the potential association between stress reduction and tobacco use reduction. We therefore hypothesize that changes in plasma PRKACA, plasma cortisol, urinary TCE, urinary NAS or urinary 6-hydroxymelatonin are potential mediators for the effect of AB-free kava in reducing TNE. To test this hypothesis, we will perform mediation analysis, where TNE reduction is the outcome variable, AB-free kava intervention is the predictor, plasma PRKACA, cortisol, urinary TCE, NAS, or 6-hydroxymelatonin is the mediator, adjusting for age, sex, race, and smoking status as covariates. The direct effects, indirect effects, and mediation proportion will be determined using the R *mediation* package. Their p-values and 95% confidence intervals will be reported. Such hypothesis, if tested positive, will provide mechanistic insight – whether AB-free kava may induce TNE reduction via relieving stress or improving sleep.

Exploratory hypothesis 4: the biological signature and biobehavioral changes are related. For a pair of biological signature and associated behavior (e.g., TNE reduction and tobacco dependence reduction, PRKACA reduction and stress reduction, or NAS increase and sleep improvement), we will compute their Pearson correlation and the corresponding p-value. This correlation analysis will be repeated for all biological signatures with the corresponding biobehavioral pairs. Such analyses will be performed both dependent and independent of kava treatments.

Plan for conducting an interim analysis and criteria for stopping rules: when 25% participants complete the study, safety data of all participants will be analyzed by DISC independently to determine whether AB-free kava intervention has any potential risk. The same practice will be implemented at 50% and 75% completion. If the adverse events are significantly higher in the AB-free kava arm than the placebo arm, the trial will be suspended to discuss with FDA and Florida Department of Health to determine whether the trial should stop.

11. STUDY MONITORING

Data and Safety Monitoring Plan Once a participant is enrolled, continuous monitoring will be conducted by Drs. Salloum and Firpi (PI and Co-Is), in conjunction with other investigators as well as IRB. Any serious adverse events as well as unanticipated problems involving risks to participants or others, will be reported to IRB, FDOH, and FDA. Our monitoring plan includes the following measures:

1. Monitor adverse events, study progression, and data quality issues; consider factors external to the study when interpreting data, such as new scientific or therapeutic developments that may have an effect on the safety of the participants or the ethics of the study; and maintain confidentiality during all phases of the trial.
2. Participants will be assessed for ALT, AST, ALP and total bilirubin at baseline, week 1, 2, 4, 8 and 12 to monitor potential acute or delayed hepatotoxic risk. Participants, whose ALT, AST, ALP or total bilirubin increases > 3 x the upper limit of normal (ULN) but ≤ 5 x ULN, will retest after 48 to 72 hours. If increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, study drug will be discontinued and participant referred for further clinical evaluation.
3. The study will undergo regular audits by a Data Integrity and Safety Committee (details in Section 12).

12. DATA INTEGRITY AND OVERSIGHT

Per UF IRB requirements, the PI will be personally responsible for conducting and supervising the conduct of human subjects research by “protecting the rights, safety, and welfare of subjects under the investigator’s care.” The PI will also ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB. The PI has voluntarily accepted these responsibilities and will fully comply with these requirements, as outlined in the UFHCC Guidance: Principal Investigator Responsibilities and Oversight.

The PI will be primarily responsible for continuous monitoring of adverse events, unanticipated problems, protocol violations, and other immediate protocol issues. The PI or their designee will collect information on subjects enrolled through the use of electronic or paper source documents, CRFs, and Informed Consent forms.

The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The study team will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data Integrity and Safety Committee (DISC). This protocol will be reviewed and monitored by the University of Florida Health Cancer Center Data Integrity and Safety Committee (UFHCC DISC) in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise, the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

In compliance with the UFHCC data and safety monitoring plan, the PI will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC CCPSP (Scientific Review and Monitoring Committee Cancer Control and Population Sciences Panel) review, which occurs prior to initial IRB approval.

UFHCC investigator-initiated protocols will be classified into one of the following categories of risk by the SRMC CCPSP (see *SRMC manual* for further details):

Level 1 – **Low risk** Investigator Initiated interventional trials.
Level 2 – **Moderate risk** Investigator Initiated or externally sponsored interventional (such as drug, biologic or device) trials using FDA approved or commercially available compounds or interventions.
Level 3 – High **risk** Investigator Initiated or externally sponsored interventional trials (such as investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
Level 4 – Complex trials involving **very high risk** to subjects and a high level of complexity such as first in human or gene transfer studies.

The risk level assigned by the SRMC CCPSP will determine the appropriate level of DISC monitoring required, with increased monitoring required for higher-risk trials.

13. DATA MANAGEMENT

Data collection for the trial will be managed through REDCap and stored on secure UF servers. Questionnaire data forms will be subject to computerized range and consistency checks. Biological data will be subject to computerized range and consistency checks as well. Initial examination of data will include descriptive statistics, frequency distributions, and histograms in order to identify outliers, missing data and check data source adequacy. This process will be supervised jointly by the PI and the lead statistician. Data will be periodically converted to SAS and R data types. Any entry error and/or inconsistency will be discussed during meetings with the study team. Quarterly statistical summaries and progress reports will be generated by the statistician for review by all investigators. To ensure participant confidentiality, all personal identifiers will be expunged from the data set.

14. CONFLICT OF INTEREST

The funded grant will evaluate AB-free kava's potential to help smokers reduce tobacco use and risk of lung cancer. The AB-free kava product to be evaluated is developed by Thorne, based on the IPs owned by Kuality Herbceutics (KH). KH has an estimated value of $400,000 on the basis of the IP and the investment to date, which is to support IP protection. There is no profit or product from KH yet. Chengguo Xing (the PI of this grant) owns 55% of the stock of KH. He also provides consultation to KH for its strategy on development.

Describe any conflict of interest relevant to this protocol. If none to note, please note “Not applicable”.

15. APPENDICES

A. Proposed measures for tobacco use, craving, addiction, stress, and insomnia
B. Schedule of events

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17. APPENDIX A:

Proposed Measures For Tobacco Use, Craving, Addiction, Stress, And Insomnia

Self-Reported Measures of Smoking Cigarettes

✓ Instructions for Filling Out the Timeline Cigarette Use Calendar

To help us evaluate your cigarette use, we need to get an idea of what your smoking was like in the past_____ days. To do this, we would like you to fill out the attached calendar. Filling out the calendar is not hard! Try to be as accurate as possible.

We recognize you won't have perfect recall. That's **OKAY**.

WHAT TO FILL IN

The idea is to record how many cigarettes you smoked for each day on the calendar. On days when you did not smoke cigarettes, not even one, you should write a "0." It's important that something is written for every day, even if it is a 0".

YOUR BEST ESTIMATE

We realize it isn't easy to recall things with 100% accuracy. If you are not sure whether you smoked 15 or 16 cigarettes or whether you smoked on a Thursday or a Friday, give it your best guess! What is important is that 15 or 16 cigarettes is very different from 1 cigarette. The goal is to get a sense of how frequently you smoked, how much you smoked, and your patterns of smoking.

HELPFUL HINTS

- If you have an appointment book, you can use it to help you recall your use.
- Holidays such as Thanksgiving and Christmas are marked on the calendar to help you recall your smoking. Also, think about how much you smoked on personal holidays & events such as birthdays, vacations, or parties.
- If you have regular patterns to your smoking, you can use these to help you recall your use. For example, some people may only smoke during social situations.

COMPLETING THE CALENDAR

A blank calendar is attached. Write in the number of cigarettes you smoked on each day. The time period we are talking about on the calendar is from_____ to _____. In estimating the number of cigarettes you smoked, be as accurate as possible.

DOUBLE CHECK THAT ALL DAYS ARE FILLED IN BEFORE RETURNING THE CALENDAR.

Before you start look at the **SAMPLE CALENDAR**.

Fagerstrom Test for Nicotine Dependence

1. How soon after you wake up do/did you smoke your first cigarette?

   1[ ]Within 5 minutes [3 points]

   2 [ ]6-30 minutes [2 points]

   3 [ ]31-60 minutes [1 point]

   4 [ ]After 60 minutes [0 points]

2. Do/Did you find it difficult to refrain from smoking in places where it is forbidden, e.g.,in church, at the library, in a cinema, etc.?

   1[ ]Yes [point]

   2[ ]No [0 points]

3. Which cigarette would you hate most to give up?

   1[ ]The first one in the morning [1 point]

   2[ ] All others [0 points]

4. How many cigarettes per day do/did you smoke?

   1[ ]10 or less [0 points]

   2[ ]11-20 [1 point]

   3[ ]21-30 [2 points]

   4[ ]31 or more [3 points]

5. Do/did you smoke more frequently during the first hours after waking than during therest of the day?

   1 [ ]Yes [1 point]

   2[ ]No [0 points]

6. Do/did you smoke if you are so ill that you are in bed most of the day?1[ ]Yes [1 point]

   2[ ]No [0 points]

Modified Cigarette Evaluation Questionnaire

If you have smoked since you last completed this questionnaire, please mark the number that best represents how smoking made you feel (1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

1. Was smoking satisfying?
2. Did cigarettes taste good?
3. Did you enjoy the sensations in your throat and chest?
4. Did smoking calm you down?
5. Did smoking make you feel more awake?
6. Did smoking make you feel less irritable?
7. Did smoking help you concentrate?
8. Did smoking reduce your hunger for food?
9. Did smoking make you dizzy?
10. Did smoking make you nauseous?
11. Did smoking immediately relieve your craving for a cigarette?
12. Did you enjoy smoking?

Brief Questionnaire on Smoking Urges

*Indicate how much you agree or disagree with each of the following statements by placing a single checkmark (like this: [✔]) by a number ranging from 1 (strongly disagree) to 7 (strongly agree). The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling**right now** as you are filling out this questionnaire.*

1. I have a desire for a cigarette right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

2. Nothing would be better than smoking a cigarette right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

3. If it were possible, I probably would smoke right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

4. I could control things better right now if I could smoke.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

5. All I want right now is a cigarette.

1 [ ] STRONGLY 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY

DISAGREE]]]]] AGREE

6. I have an urge for a cigarette.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

7. A cigarette would taste good now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

8. I would do almost anything for a cigarette now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

9. Smoking would make me less depressed.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

10. I am going to smoke as soon as possible.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

Perceived Stress Scale

For each question choose from the following alternatives:
0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

_____ l. In the last month, how often have you been upset because of something that happened unexpectedly?

_____ 2. In the last month, how often have you felt that you were unable to control theimportant things in your life?

_____ 3. In the last month, how often have you felt nervous and stressed?

_____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?

_____ 5. In the last month, how often have you felt that things were going your way?

_____ 6. In the last month, how often have you found that you could not cope withall the things that you had to do?

_____ 7. In the last month, how often have you been able to control irritations inyour life?

_____ 8. In the last month, how often have you felt that you were on top of things?

_____ 9. In the last month, how often have you been angered because of things thathappened that were outside of your control?

_____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Insomnia Severity Scale

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you haveyour total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?Not at all

Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?Not at all

Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytimefatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) =_____

your total scoreTotal score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)22–28 = Clinical insomnia (severe)

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Modified Pittsburgh Sleep Quality Index (MPSQI)

Modified Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   _____

3. During the past month, what time have you usually gotten up in the morning?

   _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or “over the counter”)?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed	
10. Do you have a bed partner or room mate?					
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week	I don't know
If you have a room mate or bed partner, ask him/her how often in the past month you have had:					
a. Loud snoring					
b. Long pauses between breaths while asleep					
c. Legs twitching or jerking while you sleep					
d. Episodes of disorientation or confusion during sleep					
e. Other restlessness while you sleep, please describe:					

Modified Ask Suicide-Screening Questions (MASQ)

Modified NIH ASQ Screening Tool

Subject ID _____

ASQ Screening Tool

1. In the past few weeks, have you wished you were dead?	◯ Yes ◯ No
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?	◯ Yes ◯ No
3. In the past week, have you been having thoughts about killing yourself?	◯ Yes ◯ No
4. Have you ever tried to kill yourself?	◯ Yes ◯ No
If yes, was it in the past 12 months?	◯ Yes ◯ No
Date Form completed	_____ (M-D-Y)
Subject Signature upon completion	_____

Additional resources : UF psychiatric clinical sites (352) 265 - 4357

Alachua County Crisis Center (352) 264 - 6789

National Suicide Hotline 1 (800) - 784 - 2433

NIH Sleep Diary

Fill out before going to bed	Today's date:								
	Number of caffeinated drinks (coffee, tea, cola) and time when I had them today:								
	Number of alcoholic drinks (beer, wine, liquor) and time when I had them today:								
	Naptimes and lengths today:								
	Exercise times and lengths today:								
	How sleepy did I feel during the day today? 1—So sleepy I had to struggle to stay awake during much of the day 2—Somewhat tired 3—Fairly alert 4—Alert								
Fill out in the morning	Today's date:								
	• Time I went to bed last night: • Time I got out of bed this morning: • Hours spent in bed last night:								
	Number of awakenings and total time awake last night:								
	How long I took to fall asleep last night:								
	Medicines taken last night:								
	How alert did I feel when I got up this morning? 1—Alert 2—Alert but a little tired 3—Sleepy								

18. APPENDIX B: SCHEDULE OF EVENTS

Visit: Procedure:	SCREENING[2] Visit 0 (4 – 21 days prior to Day 1)	BASELINE/WEEK 0 Visit 1 (Day 1)	WEEK 1 Visit 2 (7 days, +/- 3 days)	WEEK 2 Visit 3 (7 days, +/- 3 days)	WEEK 4 Visit 4 (14 days, +/- 3 days)		WEEK 8 FOLLOW UP VISIT 5 (28 days +/- 3 days)	WEEK 12 FOLLOW UP VISIT 6 (28 days, +/- 7 days)
Informed Consent	X							
Demographic Information	X							
Relevant Medical History[6]	X							
Brief Physical Exam	X				X			
CO breath test	X	X	X	X	X		X	X
Height	X							
Weight	X							
Biomarker Assessment-(blood and urine)		X	X	X	X		X	X
Labs (CMP)	X	[4]	X	X	X		X	X
Pregnancy Test (Urine)	X							
Randomization	X							
Administration of Study Drug		X	X	X				
Review and/or dispense subject Pill Diary		X	X	X	X			
Concomitant Medication Review[7]	X							
Adverse Event Review		X	X	X	X		X	X
24-h urine- supplies	X	X	X	X	X		X	
GT3X+ Wearable device (WD)[2]	X	X	X	X	X			
Questionnaires	X[3]	X	X	X	X		X	X
Exit Interview								X
In-depth Interview[5] (Post-Treatment Interview)					X			

Insert information, as appropriate, if superscripts are used within the table. Examples provided below.

Abbreviations; CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin)

1. Screening procedures performed per Standard of Care within the screening window can be used even if prior to consent.
2. GT3X+ wearable device will be provided to participants at the end of Visit 0; the wearable device will be replaced during Visit 1 – 3 by study coordinator and the device will be collected during Visit 4.

3. MASQ questionnaire only, given at screening
4. Blood will not need to be redrawn if their baseline visit is within 7 days of their screening labs.
5. Collected until completed by 25 subjects.
6. Relevant medical history is defined as any diagnosis of depression.
7. Concomitant Medications defined as all medications participant is actively taking at time of enrollment.

19. APPENDIX C: SUMMARY OF CHANGES

Protocol Version Number	Protocol Version Date	Affected Section(s)	Summary of Revisions Made
1.0	Jun. 8, 2023	-	N/A- Initial protocol
2.0	Nov. 29, 2023	Title Page	- Added Co-I Dr. Frank Orlando
		Abstract	- Removed Half-dose treatment arm - Increased sample size from 75 to 76
		Section 2	- Removed Half-dose treatment arm - Increased sample size from 75 to 76
		Section 3	- Removed Arm from Schema visual - Removed Half-dose treatment arm - Increased sample size from 75 to 76 - Added UF Consent2Share language - Added language mentioning UF Springhill Clinic site location and Dr. Frank Orlando - Minor language corrections
		Section 4	- Removed Half-dose treatment arm - Minor language corrections
		Section 5	- Added more detailed language for UF Springhill Site and UF Consent2Share Program - Increased sample size from 75 to 76
		Inclusion Criteria	- A) Minor Language Change

		Exclusion Criteria Section 6 Section 9 Section 10 Appendix B	- G) Added language for exclusionary exception --- - Removed Half-dose treatment arm - Corrected treatment group labeling language --- - Removed language mentioning Dr. Firpi - Added language for Dr. Orlando and Dr. Malaty - Clarified reporting language --- - Corrected statistical language for a two-arm trial --- - Minor change to text symbols ( ) for In-depth Interview procedure - Minor deletion of footnote language for simplification
	Apr. 15, 2024	All Protocol Mentions	- Renamed all ASQ Questionnaire (ASQ) language to Modified ASQ Questionnaire (MASQ)

2.1	May 20, 2024	Appendix B: Schedule of events	- Removed CBC w/diff from required lab collections
3.0	Sep. 10, 2024	Section 3	- Added language to clarify study window for Post-Treatment Interview. If missed, will not result in a deviation - Amended questionnaire list. Minor modification to Pittsburgh Sleep Quality Index. Now MPSQI. - Added NIH Sleep Quality Diary to questionnaire list. Will not result in a deviation if missed. - Added language to clarify Post-Treatment Interview is optional. Collection will stop after 25 subjects have completed it.
		Section 5	- Added new inclusion criteria regarding potential participants prior usage of Kava and participation in other Kava trials.
		Section 6	- Randomization language amended to more accurately reflect current procedures
		Section 7	- Language added to define relevant medical history collection.
		Section 9	- Language added to clarify the AE reporting window and REDCap reporting criteria for Serious and Non-Serious AEs.
		Section 15	- Minor formatting change for Appendices
		Appendix A	- Added entry for MPSQI. It was not previously included in Appendix A but was mentioned in prior protocol version. - Added entry for NIH Sleep Diary
		Appendix B	- Amended event windows to clarify that visits are scheduled from date of prior check-in following Visit 1 (Week 0)

			- Removed collection of concomitant medications at all visits except screening. - Added 'Pill' to diary language to avoid confusion with sleep diary - Added footnote #5 to clarify Post-Treatment interview only collected until completed by 25 subjects. - Added footnote #6 to define Relevant Medical History collection. - Added footnote #7 to define concomitant medications _____