The Effectiveness of Ginseng in the Treatment of Major Depression

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**Summary:**

Extracts of Ginseng are believed to be able to treat depression, but with no significant studies into the effects of Ginseng on depression we cannot have evidence for this, therefore we will test the efficacy of Ginseng as compared to a placebo.

**Background of Study:**

Herbal remedies are very common in the world of alternative medicine to treat various physical ailments with very limited scientific and clinical backing to their efficacy1. One of these is Ginseng, an herb that is most often consumed in the form of a tea. Ginseng is purported to improve mental and physical health as well as improve “quality of life”2. There have been several clinical studies to see the effect that Ginseng has on the quality of life for an individual, but no tests on the effects of Ginseng on depression have been conducted yet2. The purpose of this study is to determine the efficacy and safety of consuming a Ginseng extract for the purposes of treating Major Depression.

**Objectives of Study:**

1. Primary Objective: The primary objective is to compare the efficacy and safety of a standardized extract of Ginseng with placebo in outpatients with major depression.
2. Secondary Objectives:
   1. To assess Ginseng’s effects on anxiety.
   2. To assess Ginseng’s effects on general health, particularly the blood pressure and heart rate of the subject.
   3. To assess whether Ginseng causes nervousness, insomnia, or changes in blood pressure for the subject.
3. Subgroup Hypothesis:
   1. To assess whether Ginseng will be more effective on those with more mild depression (HAM-D score of 22 or lower).
4. Adverse Effects:
   1. Ginseng is said to cause nervousness by those who consume it.
   2. Ginseng is said to cause insomnia by those who consume it.
   3. Ginseng is said to cause changes in blood pressure by those who consume it.

**Study Design**

1. Formal Study Design: The formal study design is that of a “parallel design” using a placebo control group where both the control and the treatment groups are randomized.
2. The study will primarily be conducted with the assistance and on the grounds of 10 university hospitals. All of the patients are to be provided with written consent forms as well consent will have to be obtained from each participating hospital.
   1. Inclusion Criteria:
      1. The subject must be an adult (18 or older).
      2. The subject must have been diagnosed with a depressive disorder and has to have a HAM-D Score of at least 20.
      3. The subject must be healthy (i.e. non-diabetic, non-HIV-positive, no cancer, etc.).
   2. Exclusion Criteria:
      1. The subject must not had a cognitive disorder, post-traumatic stress disorder, eating disorder, or a substance abuse disorder in the last six months.
      2. The subject must not had a panic disorder in the last year.
      3. The subject must not have a current or past history of bipolar disorder, any psychotic disorder, or borderline, antisocial, or schizotypal personality disorder.
      4. The subject must not have participated in an experiment or clinical trial within the past month (30 days).
      5. The subject must not take anticoagulants.
      6. The subject must not be pregnant, planning to become pregnant, or currently nursing.
3. Power Calculations:

For the power calculations we looked to previous studies to see what we believed the Ginseng extract would be capable of. We believe that Ginseng would have a similar effect to St. John’s Wort, which is to say very little effect, thus we used estimates from the Shelton et. al. article3 for the estimates of the effectiveness of Ginseng. From the article we can gather that St. John’s Wort was found to have an effective response rate of about 26.5%, whilst the placebo had an effective rate of about 18.5%. This give us our and our , which also indicated that the difference between these success rates is . This brings us to elements that we do not have to estimate. The study is to bring in 1500 subjects from 10 University hospitals with 750 subjects being part of the control group and 750 subjects being part of the treatment group, giving us and . Lastly for our calculations we are using for this experiment. We want it to be relatively low so that the results are more likely to be accurate.

We had considered using the drug “nefazone” () for a basis for the Ginseng extract, but this was seen as much stronger and more able to combat depression as compared to Ginseng so we opted not to use it. We had similar considerations for the drug “clovoxamine” ( and ) but we also saw this drug as far more effective than what we believe Ginseng to be capable of.

Using the PS Power and Sample Size Calculator we used the dichotomous tab to find the power of the study. Under this tab we indicated that we wanted the power, then that the variables were independent, that the comparison was between two treatments (prospective), that the alternative hypothesis would be expressed as two proportions, and that we would be utilizing Fisher’s Exact test. By using these settings we obtained and generated the following block below:

We are planning a study with 750 experimental subjects and 750 control subjects. Prior data indicate that the failure rate among controls is 0.185. If the true failure rate for experimental subjects is 0.265, we will be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) .859. The Type I error probability associated with this test of this null hypothesis is 0.01. We will use a continuity-corrected chi-squared statistic or Fisher’s exact test to evaluate this null hypothesis.

**Enrollment of Participants**

1. Informed Consent:

It is currently believed that Ginseng may have properties that could be used to treat depression. The purpose of this study is to assess whether Ginseng can actually be used to treat depression, as measured by the Hamilton Depression Score. For this study we will have 1500 subjects, each of which will be older than 18, have a Hamilton Depression Score of 20 or more, and have been discharged from psychiatric care for a major depression.

First, you will be assessed using the Hamilton Depression Score so that we have a baseline of your depression. Secondly, you will be prescribed with an eight week supply of Ginseng tablets which are to be taken as described on the bottle. Thirdly, you will return at the then of week two and week eight for post-baseline assessments using the Hamilton Depression Score. The risks of taking Ginseng are minor. The consumption of Ginseng is associated with mild nausea, mild nervousness, and changes in blood pressure, all of which are possible results of this treatment. Any discomfort should be notified to the physician interviewer.

All participants will be assessed using the Hamilton Depression Score and will have their results revealed. Patients will be given a Ginseng treatment that is believed to treat depression. If you refuse to partake in the treatment, then the initial assessment will still be performed by the staff. All collected data is to remain confidential and private. The data will only be used for analysis in the experiment. If a psychiatric emergency were to occur as a result of the experiment, then psychiatric treatment will be provided to subjects for six months after the end of the experimental treatment at no cost to the subject.

If you want to ask or talk to anyone about this research study, please call Dr. Larry Young at 732-555-5555, who is in charge of Psychiatric Screening for the trial. Participation is voluntary and the subject may quit the study at any time. There is no obligation and leaving at any time will not relinquish the compensation of the experiment.

1. Assessment of Eligibility:

The assessment of eligibility will be performed by site staff at a point before the beginning of the trial and after the progression of 12 months into the recruiting process. This will involve the subject filling out several forms for medical information as well as performing some physical and mental tests with the subject. This is to be done at the discretion of the site but is required before the beginning of the trial (with earlier screening rather than later). Firstly the site staff should review the study with the subject and obtain written informed consent from the subject. At this point the relevant information should be given to the subject and the procedure both for the current session as well as all future sessions should be clearly laid out.

Review the medical history of the subject, including current and past medications, surgeries, and drug use, and record relevant findings. This information must come from the subject directly in a written form. Medication history would include any medication prescribed or recommended by a licensed medical professional including over-the-counter and herbal medicines. Drug use should include the consumption of alcohol, caffeine, and tobacco products. Along with all medical records and history, the subject’s demographics (race, sex, age, etc.) should be transcribed for records. The subject will be tested using the Hamilton Depression Score test which will be administered by site staff, this will be used for eligibility but not for the baseline. Lastly women of childbearing potential will be administered a urinary pregnancy test. A refusal for any of these test will render the subject ineligible for the trial.

At this point the eligibility of a subject should be determined with the requisite number of subjects required of the site being selected. The subjects selected for the trial should then be assigned a unique number for the site at which they are to be enrolled. This number will be used for identification and for randomization. The number will have an identifier for the clinic appended to the front (i.e. patient 1 at clinic 1 would become 100001).

1. Baseline Examination:

After the processes of recruitment and determining the eligibility of subjects the final selection of the subjects will have been performed. The subject ID will be used to randomize the subjects into the control and treatment groups, although the baseline examination is the same for each of the two groups. The subjects will be called in by order of their ID and will be given the baseline assessment. The assessment is to be carried out on Monday, 2 October 2023, and will represent Day 1 of the trail. At the outset of the assessment a review of all consent documents and all subject rights will be covered, as well as giving a current description of the trial. It is at this time that a review of all non-demographic information will be performed to make sure that not only the information is consistent, but that the subject has not undergone any changes in that time.

The subject will then begin the main part of the baseline assessment, starting with a form being given to the subject using the HAM-D Score to determine a baseline score for the subject. At this point subjects which have shown significant improvement (a drop of 2 HAM-D Score or more) without the treatment will be dropped from the trial, but a baseline will still be taken from them. We will also test subjects immediately after using the HAM-A Score (Hamilton Anxiety Score) test to get a baseline for anxiety. As the HAM-A Score test discusses nervousness as one of the indicators of anxiety, we can use this score as the baseline for nervousness in the subject. After the mental examinations we will then begin the physical, which will be a standard physical with measures of heart rate and blood pressure and will be performed by an RN (Registered Nurse) who is to be part of site staff. As part of the physical we will also inquire about the length of sleep that the subject attained the night before, as well as inquiring about the quality of said sleep. These measurements will be used as the baseline for the trial, particularly for the baseline of heart rate, blood, pressure, and insomnia.

After this point the subject will be informed that they are to be given a number of tablets of Ginseng extract by the RN (regardless if the subject is in the treatment or control group) and will be given a record sheet that will be filled out on their own time. The subject will be instructed in consumption of either the treatment or placebo, as well as how to fill out the sleep sheet, by the RN. At this point they will be given both the tablets (either the treatment or a placebo based on their number) and the sheet and the next subject will be sent into the room. Several RN should be doing this at once across several rooms.

For the HAM-D and HAM-A tests we will use sheets that we can find at: <https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf> and <https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-ANXIETY.pdf>. The physical form will be a generic annual physical form which can be obtained here: <https://www.pchc.org/images/PDFs/Forms/Annual-Physical-Exam-Form-with-letter.pdf>. Sections related to lab testing as well as other test which would require bloodwork or outside expertise will be either redacted or ignored during the proceedings. For the sleep sheet we will use the National Sleep Foundation’s Sleep Diary which can be found here: <https://www.sleepfoundation.org/sleep-diary/SleepDiaryv6.pdf>.

1. Randomization Approach: In this trial we will primarily be utilizing simple random sampling at each individual site. The randomization process will be performed by each of the individual hospitals, where they will take the selected sample of patients and split them into control and treatment groups using the simple random sampling. To achieve this end we will be utilizing a random number generator program and the ID of each subject. The allocation schedule will be handled directly by each of the hospitals and can be broken under emergency circumstances. As the subgroup of less depressed subjects is likely to make up a large percentage of the subjects in this trial, measures to ensure a large number of subjects form the subgroup being present in both the treatment and control groups will be unnecessary.

**Intervention**

1. Description and Schedule

Each subject will go through a process similar to the baseline examination at each assessment. The subject will begin by giving the RN access to their sleep log as well as to their pill bottle so that compliance might be checked, records may be recorded, and the tablets are to be restocked. During this time the subject will fill out the HAM-D and HAM-A tests and will give to the RN as well before proceeding to the physical. The subject will then be tested by the RN using the form indicated above, particularly blood pressure and heart rate. The subject will then be restocked with new tablets and will be informed of when the next assessment will take place. The pill bottle will be filled by a member of the study so that neither the subject, nor any member of site staff know the true nature of the subject’s treatment. If the subject is part of the treatment group they will receive a tablet with 300 mg of Ginseng extract, f they are part of the placebo group then they will receive a tablet flavored to resemble Ginseng extract. The subject will then take the tablets as they have been instructed to do, taking the tablet in the morning preferably before breakfast. They will also have to fill out their sleep log in the morning, preferably just after waking up.

If the subject is terminated early then only the sleep logging, HAM-A and HAM-D testing, and the physical will occur on the termination session and there will be no further sessions.

To ensure that both the site staff and the patients remain blind to the nature of the experiment, only a member of the study, namely one of the university coordinators, is allowed to know who is to receive the treatment or placebo. The pill bottles are only to be filled by a member of the study using the subject’s ID to determine which medication they are to receive. This process should be done in an enclosed space or office to guarantee that neither the site staff nor subject learn the designation of any subject.

1. Measures of Compliance

Compliance will be assessed primarily through the count of the tablets at each follow up session and checking the sleep records of each subject. The subject will only be given enough tablets for the time between each session, but will be given the full sleep log from the start of the trial. The sleep log must be filled out in its entirety by the subject, but the part that is to be used by the trial is the section involving the length and hours of sleep. At the end of the session the subject will be granted more tablets to last them until the next session.

In hopes of reducing the number of people breaking compliance those who complete the trial or are removed due to circumstances detailed below will be given six months psychiatric treatment at the behest of the study. This will be specifically given through the psychiatric center at the University Hospital.

A lack of compliance will result in the subject being removed from the trial and may result in the subject losing out on the benefits offered. If non-compliance was brought about due to outside, emergency circumstances (such as a medical or psychiatric emergency), due to an unexpected pregnancy, or due to an adverse reaction of the trial being too sever for the subject (such as an inability to sleep) the subject will be still be given the offered benefits. If the subject willingly breaks compliance for any other reason they will lose all offered benefits. If circumstances fall outside of these conditions then it will be on the discretion of site staff on whether the subject should retain the benefits.

1. Concomitant Treatments

Any form of treatment or medication must be revealed to the study beforehand to ascertain whether the subject remains viable. If the subject is no longer viable then involvement is over and they will either be marked ineligible or removed from the trial. If they are still viable then they should take the Ginseng tablets at least an hour before they take any other medications. Any questions on whether a subject is viable should be directed a Dr. Michael Jones, contact information is at the bottom of the sheet.

1. Unmasking the Study

If a medical emergency should arise, psychiatric or otherwise, the subject should be treated immediately with both the subject and all relevant medical professionals being unmasked in the study. From this point onwards they will no longer be part of the trial but the data already collected from them will be considered.

**Follow Up Visit Description and Schedule**

For the HAM-D and HAM-A tests we will use sheets that we can find at: <https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf> and <https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-ANXIETY.pdf>. The physical form will be a generic annual physical form which can be obtained here: <https://www.pchc.org/images/PDFs/Forms/Annual-Physical-Exam-Form-with-letter.pdf>. Sections related to lab testing as well as other test which would require bloodwork or outside expertise will be either redacted or ignored during the proceedings. For the sleep sheet we will use the National Sleep Foundation’s Sleep Diary which can be found here: <https://www.sleepfoundation.org/sleep-diary/SleepDiaryv6.pdf>. For concomitant medications the name a dosage will be written on the physical sheet and will be immediately reported to the

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Visit | Screening | Baseline | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 |
| Visit Date/Window | 6/3/2023-9/29/2023 | 10/2/2023-10/4/2023 | 10/9/2023-10/11/2023 | 10/16/2023-10/18/2023 | 10/23/2023-10/25/2023 | 10/30/2023-11/1/2023 | 11/6/2023-11/8/2023 |
| Informed Consent | X | X |  |  |  |  |  |
| Assign ID | X |  |  |  |  |  |  |
| Medical History | X | X |  |  |  |  |  |
| Inclusion/Exclusion Criteria | X |  |  |  |  |  |  |
| Concomitant Medications | X | X | X | X | X | X |  |
| Physical Exam | X | X | X | X | X | X | X |
| HAM-D and HAM-A Testing | X | X | X | X | X | X | X |
| Urinary Pregnancy Test | X | X |  |  |  |  |  |
| Sleep Logging |  | X | X | X | X | X | X |
| Randomization | X |  |  |  |  |  |  |

study pharmacist.

**Ascertaining Response Variables**

1. Training: The training for the trial will be conducted in the respective hospitals of each site and will require no additional travel on the part of the hospital staff. This will occur in the one of the main conference rooms of the respective hospital (updates will be emailed to involved staff with the specific room for each site). The training for the recruitment process will begin on Friday, 1 July 2022, and will consist of 1 day of explaining the goals, recruitment protocol and schedule, and inclusion/exclusion criteria to the staff. A second session will begin on Thursday, 28 September 2023, and will consist of intervention protocol and schedule, subject retention, safety protocol, and follow-up protocol. The first of these meetings will occur over 1 day, the second meeting will take up to 2 days but will likely not take that entire time.
2. The Primary Investigator of each site will be responsible for ensuring that the stud is conducted in accordance with protocol, good clinical practice, and all regulations. They will also be responsible for all recorded data being valid. To achieve this objective, the study will be monitored and reviewed on a monthly basis by members of the study team.

Site monitoring will be conducted to make sure that the rights and safety of the subjects are protected, that the data is verifiable, complete, and accurate, and that the conduct of the trial is in accordance with the protocol and with regulations. This observation will involve observation of operations as well as a review of all materials related to the trial.

1. Mechanisms to Identify/Reduce Dropout: To reduce dropout we have provided six months psychiatric care (to begin at the end of the trial) all subjects who complete the trial. This will be rewarded only to those who complete the trial to its entirety or those who must leave the trial early due to circumstances out of their control (see measures of compliance above).

**Data Analysis**

For baseline demographic and clinical characteristic differences between the treatment group and the placebo group we would begin by using an independent t-test to determine the difference between the two groups.

In terms of the primary efficacy analysis, however, we are to use a linear regression model of subject HAM-D to describe the efficacy of both the placebo and the Ginseng extract over the 8-week trial. The model would be used to show the change in HAM-D scores over time for each patient based directly on all available data (baseline and weeks 1, 2, 4, 6, and 8) for each subject. The base model will include the progression over time, the effect of the site, and the treatment received by the subject. Three other versions of the model will also be created: the first will be two models separated from each other by treatment group and placebo group, the second will only include the treatment/placebo group and the time ignoring the site, and the third will only include those with a baseline HAM-D score of 22 or lower.

We will run the exact same kind of analysis for the HAM-A data, creating several regression models to compare the effects of the treatment and placebo. The base model will include the progression over time, the effect of the site, and the treatment received by the subject. Three other versions of the model will also be created: the first will be two models separated from each other by treatment group and placebo group, the second will only include the treatment/placebo group and the time ignoring the site, and the third will only include those with a baseline HAM-D score of 22 or lower (despite the fact that this is a measure of HAM-A).

For blood pressure, nervousness score (an extract of the HAM-A test), heart rate, and sleep times a simple linear regression will be performed for each, creating a model for the change in the dependent variables (listed at the beginning of this sentence) based on the progression of time, the treatment of the subject, and the site of the subject. Each of these will be used in the analysis of their respective values.

No analysis is to be done until the conclusion of the trial, at that point all the data is to be analyzed.

**References**

1. Herbal Remedies in Psychiatric Practice by Wong et. al. Arch Gen Psych 1998;55:1033-44
2. Effects of a Standardized Ginseng Extract on Quality of Life … a Double-Blind Placebo Controlled Trial” by Wiklund et. al. Int J Clin Pharm Res 1999: 29(3) 89-99
3. Effectiveness of St John’s Wort in Major Depression… A Randomized Controlled Trial by Shelton et. al. JAMA 2001; 285:1978-1986

**Appendix A - Organization and Administrative Responsibilities**

1. Research Team: These are the members of the trial who are not directly staff of any of the University Hospitals.

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| Name | Role | Description |
| Eric Cartaya | Primary Investigator | Responsible for all study related issues. |
| Michael Jones, MD, Larry Young, MD, Gavin Free, MD | Co-Investigators | Data management and analysis; involved in the screening and follow up with subjects. |
| Karl Jones | Project Coordinator | Data management and analysis; organizes the University coordinator and manages trial schedule. |
| William Talty, Rachel Straub, Eileen Gillen, Rosemarie Hogan, MD/PHD, Maria Gonzalez, Adam Kovic, Daniel Markos, Craig Williams, Kim Wong, Kyle Thompson | University Coordinators | Data collection and analysis; involved in screening subjects, gathering consent, randomizing subjects, and following up with subjects; also keeps the site staff blind to subject groups. |
| Erica Lee | Biostatistician | Data management and analysis. |
| Sean McAvoy, Pharm.D | Pharmacist | Advisory role on the subject of concomitant treatments. |

1. Data Safety and Monitoring Board: This board should consist of Eric Cartaya, Dr. Sean McAvoy, Dr. Michael Jones, Dr. Larry Young, Dr. Gavin Free, Erica Lee, and Karl Jones. At least four members, which must include Eric Cartaya, Karl Jones, and Dr. Gavin Free, must meet once a week to discuss the data and safety of the project. They will meet on the Thursday immediately after the data collection window for the week ends and all of the data has been collected for the project. Preferably all members would show up and each mentioned member must meet with the project at least once every month.