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Rhodiola Rosea Therapy for Major Depressive Disorder: A Study Protocol for a Randomized, Double-Blind, Placebo- Controlled Trial

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Abstract

Background: *Rhodiola rosea* (*R. rosea*), a botanical of both western and traditional Chinese medicine, has been used as a folk remedy for improving stamina and reducing stress. However, few controlled clinical trials have examined the safety and efficacy of *R. rosea* for the treatment of major depressive disorder (MDD). This study seeks to evaluate the safety and efficacy of *R. rosea* in a 12-week, randomized, double-blind, placebo-controlled, parallel group study design.

Methods/Design: Subjects with MDD not receiving antidepressant therapy will be randomized to either *R. rosea* extract 340-1,360 mg daily; sertraline 50-200 mg daily, or placebo for 12 weeks. The primary outcome measure will be change over time in the mean 17-item Hamilton Depression Rating score. Secondary outcome measures will include safety and quality of life ratings. Statistical procedures will include mixed-effects models to assess efficacy for primary and secondary outcomes.

Discussion: This study will provide valuable preliminary information on the safety and efficacy data of *R. rosea* versus conventional antidepressant therapy of MDD. It will also inform additional hypotheses and study design of future, fully powered, phase III clinical trials with *R. rosea* to determine its safety and efficacy in MDD.

Keywords: *Rhodiola rosea*; Major depressive disorder; Depression; Herbal therapy; Botanical therapy; Alternative medicine

Background

Major Depressive Disorder (MDD) is a common psychiatric condition that affects an estimated 350 million adults worldwide [1]. In the US, the lifetime prevalence for MDD is estimated at 16.5% with the 12-month prevalence estimated at 6.7%. Approximately 70% of MDD cases are classified as mild to moderate in severity [2,3]. The annualized healthcare expenditure in the United States for treating MDD with conventional therapy is estimated at more than $120 billion [4,5]. Because of its substantial impact, novel therapies for MDD need to be developed.

Over the last three decades, the use of herbal remedies has become widespread [6]. However, the lack of pharmacological and clinical data on the majority of herbal medicinal products is a major impediment to the integration of herbal medicines into conventional medical practices. Many challenges exist when evaluating the effectiveness and safety of these herbal products using Randomized Controlled Trials (RCTs). For example, many herbal products have multiple ingredients with varying concentrations of the therapeutic compounds between products, making quality control and the selection of dosage regimens difficult; because modern medicine and herbal medicine diagnosis use different approaches to understand health and disease, therefore choosing the appropriate inclusion and exclusion criteria can be difficult; furthermore regulatory requirements such as filing an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) have to be met in order to conduct a large Phase III trials [7]. Despite these challenges, rigorous research is needed to inform evidence-based use of herbal medicine.

Rhodiola rosea (R. rosea), also known as arctic root, roseroot and golden root, has been used as a traditional folk remedy in Europe and a traditional Chinese medicine in Asia for enhancing endurance, work performance, fertility, and longevity, and for reducing fatigue, depression, anemia, cancer, and altitude sickness [8,9]. Data from the animal and human studies suggest that *R. rosea* may also have adaptogen properties via its modulation of central stress response mechanisms through its effect on central neurotransmission and neuroendocine function. Specifically, *R. rosea* appears to have a positive impact on hypothalamic-pituitary-adrenocortical (HPA) axis activity which, in turn, modulates the central immune-response system.

This action is thought to play a key role in modulating stress and the body's ability to adapt to it [10]. *R. rosea* also appears to modulate the central stress response via its effect on central biogenic amine neurotransmission and by increasing blood brain barrier permeability to precursors of dopamine (DA) and serotonin (5-HT) [8]. *R. rosea* also appears to increase β-endorphin levels, protect against stress-

induced endorphin elevation [11], and modulate release of HPA axis peptides.

This modulatory effect on excessive opioid and catecholamine response to stress (which may also activate humeral and cell-mediated immunity), may modify normal tolerance to stress [8]. Thus, *R. rosea* may exert its antidepressant effect by enhancing central neurotransmission and reducing or modulating excessive HPA axis activity [12].

Informed by these preliminary findings, we propose to investigate the antidepressant activity of *R. rosea* extract in patients with MDD. To date, there have been no randomized clinical trials of *R. rosea's* antidepressant activity compared to that of conventional antidepressant drug therapy in MDD. This study seeks to obtain preliminary efficacy and safety data to determine the necessary effect size to conduct a fully powered, parallel group comparison of *R. rosea's* antidepressant activity in adults with MDD.

Specific Aims and Hypotheses

Primary study aim

To examine the safety and efficacy of short-term *R. rosea* versus sertraline or placebo therapy in subjects with MDD. We hypothesize that *R. rosea* will have superior efficacy versus placebo and comparable efficacy versus sertraline. The primary outcome measure is change over time in mean 17-item Hamilton Depression Rating (HAM-D) score.

Secondary study aim

To compare the safety and quality of life (QOL) profile of *R. rosea* versus sertraline or placebo. We hypothesize that *R. rosea* will have a superior tolerability profile versus sertraline, and a similar tolerability profile versus placebo. We also hypothesize that *R. rosea* will have superior QOL and sexual performance profile versus sertraline or placebo. Secondary outcome measures of safety and QOL measures include: (i) frequency, duration, and severity of adverse events (AEs), (ii) frequency of serious AEs, (iii) frequency of dosage reduction; (iv) frequency of treatment discontinuation, and (v) QOL and sexual performance measures.

Methods/Design

Study design

This is a 12-week randomized, double-blind, placebo-controlled, parallel group study of *R. rosea* to treat MDD of mild to moderate severity. Subjects will be randomized to one of three treatment conditions: *R. rosea* extract 340-1,360 mg daily; sertraline 50-200 mg daily; or placebo. This study has been approved by the University of Pennsylvania Institutional Review Board.

Study population

Target population will be adult subjects 18-70 years old with Axis I diagnosis of MDD of mild to moderate severity in accordance with the Diagnostic and Statistical Manual of Mental Disorders - Fourth Revision (DSM IV). Table 1 displays the study inclusion and exclusion criteria, source of study materials, and role of study personnel. The principal investigator, who is a physician scientist, will review all eligibility documents and determine whether subjects are suitable for participating in the study. Assuming a 20% lost-to-follow-up rate of subjects who have been randomized into the study, we expect to recruit a total of 58 subjects in order to reach a proposed sample size of 48 subjects (or 16 subjects per treatment condition).

Inclusion Criteria	Source	Assessor
Age ≥ 18 years	Self-report	Study nurse, Study Coordinator
DSM IV Axis I diagnosis of mild to moderate MDD	Structured Clinical Interview for DSM-IV (SCID)	Study nurse, Diagnostician
Clinical Global Impression rating of 3 ('mild') or 4 ('moderate')	Clinical Global Impression (CGI)	Study nurse
17-item Hamilton Rating Scale for Depression score ≥10	Hamilton Rating Scale for Depression	Study nurse
Not receiving other MDD therapy	Baseline visit	Study nurse
Able to provide signed informed consent	Baseline visit	Study nurse, Study Coordinator
Final, overall eligibility		Principal Investigator

Table 1: Inclusion Criteria and Source Document

Study drug

R. rosea SHR-5 extract

We will utilize pharmaceutical grade *R. rosea* SHR-5 extract standardized to a content of rosavin 3.07% and rhodioloside 1.95% (Swedish Herbal Institute [SHI], Gothenburg, Sweden). The R. rosea extract will be provided with a current certificate of analysis [COA] to document its purity and suitability for human use. The active ingredients of *R. rosea* extracts are tyrosol (syn. salidrosol) [2-(4-hydroxyphenyl)ethanol], and the phenolic glycosides, rhodioloside (syn. rhodosin, salidroside) [2-(4-hydroxyphenyl)ethyl-1-β-D-glucopyranoside] and rosavin (syn. Cinnamyl alcohol β-vicianoside) [3-phenyl-2-propenyl-O-(α-L-arabinopyranosyl-(1-6)-β-Dglucopyranoside) [13-17].

The FDA has granted us an IND 106,350 approval for *R. rosea* SHR-5 extract use in MDD in a "Safe to Proceed" letter on September 16, 2009.

Sertraline hydrochoride

We will use commercially available Sertraline HCl 50 mg tablets manufactured by NorthstarRx LLC Pharmaceutical, Memphis, TN. The NDC number is 16714-0612-04.

Placebo

Pure pharmaceutical-grade lactose monohydrate NF (Spectrum® Quality Products, New Brunswick, NJ), rather than *R. rosea* extract or sertraline, will be packed into the placebo capsule to give the placebo capsule a 'feel' similar to the *R. rosea* and sertraline capsule.

Drug preparation and blinding procedure

Study drug will be prepared by Penn Investigational Drug Service (IDS) and dispensed in identically appearing capsules of *R. rosea* SHR-5 extract 340 mg, sertraline HCl 50 mg, or placebo.

Study drug will be packaged in air-tight, tamper-sealed bottles containing 30, 60, or 120 capsules each. Stock gelatin capsule shells that accommodate the largest dosage formulation of study drug will be used. The blinded capsule shells will be certified to be contaminant-free and BSE-free at the time of purchase. Capsules will be hand-filled with *R. rosea* extract (or sertraline) that has first been inspected by a licensed pharmacist. Capsules will then be back-filled and lightly packed with pharmaceutical-grade lactose monohydrate NF (Spectrum® Quality Products, New Brunswick, NJ). The capsule shells will then be sealed, dusted with sodium chloride to remove outside traces of powder, then packed, sealed and assigned an internal IDS lot number that is unique for each batch. Study drug will then be packaged in TampAlert™ white polyethylene jars of 60 or 120 mL capacity with tamper-evident inside seals and child-resistant opaque caps (EPS®, Inc., Ivyland, PA).

Placebo capsules will be prepared in a similar fashion to that described above, using identical gelatin capsule shells. However, pure lactose monohydrate NF, rather than *R. rosea* extract or sertraline (with or without additional lactose monohydrate filler), will be packed into the placebo capsule to give the placebo capsule a 'feel' similar to the *R. rosea* and sertraline capsule. The capsule filling procedure will be similar to that used for the *R. rosea* and sertraline capsules previously described, except that a larger amount of lactose monohydrate will be used and there will be no *R. rosea* or sertraline present in the area at the time of preparation. The amount of lactose monohydrate NF used per capsule will be determined by the size of the capsule that is needed for the largest dose of active study product, so that all capsules appear identical. The lactose monohydrate will be used by itself with no additional additives when preparing placebo capsules.

Drug administration procedure

Study drug will be administered in a dose escalation fashion. Therapy will be initiated at one capsule daily for the first 2 weeks. Subjects with ≤ 50% reduction in total HAM-D score (versus baseline) after 2 weeks of therapy will have their dose increased to 2 capsules daily during weeks 3 and 4 of therapy. Subjects who continue to have ≤ 50% reduction in HAM-D score (versus baseline) after 4 weeks of therapy will have their dose increased to 3 capsules daily during weeks 5 and 6 of therapy. Subjects who continued to have ≤ 50% reduction in HAM-D score (versus baseline) after 6 weeks of therapy will have their dose increased to 4 capsules daily during study weeks 6 through 12 of therapy. Subjects who are unable to tolerate the assigned dose of study drug may have their dosage reduced to a minimum of 1 capsule daily. Subjects who are unable to tolerate a minimum dose of 1 capsule daily will be discontinued from the trial.

Blinded study drug will be dispensed at each study visit. A drug accountability log will be maintained and pill count will be performed at each study visit.

Subject recruitment

Subjects will be recruited from media and print advertisements targeting ethnic and racially diverse populations. Additionally, subject will be recruited from collaboration with primary care practices in the community. Subjects will be provided informed consent at the intake evaluation.

Initial subject contact will be made via telephone triage performed by a trained study coordinator who will elicit general information. After the initial phone contact, subjects will be given an appointment for an intake evaluation. If the subject meets criteria for mild or moderate MDD and does not meet other medical or psychiatric exclusion criteria, a study consent visit will be scheduled.

Randomization and stratification procedure

A blocked randomization with varying block sizes will be used. First, we will randomly select a block size from among a small set of block sizes. Then, we will randomly permute the group numbers within that block. We will generate random numbers and permute the numbers within each block using the random number generator and user written code for STATA software. The randomization is done independently of the researchers.

Study procedures

Diagnostic and clinical outcome measures:

(a) Structured Clinical Interview Diagnosis (SCID I/P) for DSM IV Axis I disorders [18]: will serve as the primary instrument for diagnostic case ascertainment. The most recent version of the SCID now contains several specifiers of MDD subtypes including those with melancholic, atypical, and psychotic features.

(b) HAM-D [19,20]: is a validated, clinician-rated instrument for ascertaining the severity of MDD symptoms. It performs consistently across diverse racial and ethnic groups [21]. We will perform the HAM-D according to the structured interview guide, modified to retain the original order of the items [20]. The HAM-D will serves as the primary outcome measure.

(c) Clinical Global Impressions (CGI) [22]: is a validated, clinician-rated measure of global symptom severity (CGI/S) and symptom change (CGI/C) of MDD. It is rated at the completion of each study evaluation. The CGI/S and CGI/C ratings will serve as secondary outcome measures.

(d) Beck Depression Inventory (BDI) [23]: is a validated, patient-rated instrument that is widely used to ascertain the presence and severity of depressive symptoms, and their change over time. It will serve as a secondary outcome measure.

(e) Psychological General Well Being Index (PGWB) [24]: is a patient-rated measure of 6 health-related QOL domains: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The PGWB index provides an overall measure of well-being in addition to the other domains. It will serve as a secondary outcome measure.

(f) Modified RUSH Sexual Inventory (RUSH) [25]: is a patient completed rating of sexual function and satisfaction. It will be used to assess current sexual health and changes in sexual health over time. It will serve as a secondary outcome measure.

(g) Treatment Emergent Symptom Side Effect (TESS) [26]: is a clinician-rated profile of adverse events. The TESS includes the date of AE onset and cessation, severity of AE (i.e., mild, moderate, severe), relationship of the AE to treatment or study procedure (i.e., none, possible, probable, definite), and outcome. AE information is obtained

via spontaneous patient report, doctor query, and changes in physical and laboratory findings. It will serve as a secondary outcome measure. Possible AEs might include weight gain/loss, insomnia/hypersomnia, sedation, sexual dysfunction, gastrointestinal complaints, and anxiety.

(h) Columbia Suicide History Form (CSHF) and Columbia Suicide Severity Rating Scale (CSSRS) [**27**]: are validated, clinician-rated instruments that ascertain past and current suicide risk, ideation, and behavior. They will serve as secondary outcome measures.

(i) Expectations for Therapy Inventory (ETI): is a 4-item, patient-rated measure of expectations of outcome modified from the Acupuncture Expectancy Scale [28,29], a validated instrument to measure outcome expectancy related to treatment. .

(j) Credibility Rating of Blinding Index (CRBI): is a patient-rated questionnaire adapted from prior complementary and alternative medicine (CAM) acupuncture studies [30,31]. It will serve as a secondary outcome measure of blinding validation.

(k) Expectation of Side Effects of Therapies and (l) Expectation of Therapeutic Effects: are patient-rated measures of expectations of side-effects and therapeutic effects of the study drug. Both assessments will serve as additional measures to test if early expectancies affect therapeutic effects.

(m) Insomnia Severity Index (ISI) [32,33]: a 7-item validated self-reported instrument to measure insomnia.

(n) Brief Fatigue Inventory (BFI) [34]: a 9-item validated self-reported instrument to measure fatigue.

Study visits

Visit 1 - Intake Evaluation (to determine eligibility)

Initial subject contact will be made via telephone triage. General information about referral source, subject demographics, clinical variables (e.g., duration of current episode, current treatment, medical disorders), and the presence of suicidal ideation will be obtained. A brief description of the procedures will be provided, and the subject will be provided with an appointment for an intake visit. At this appointment, informed consent and initial clinical data will be obtained.

Concurrent therapy with an antidepressant, mood stabilizer, stimulant, or anti-psychotic agents will not be permitted during the trial. After providing informed consent, subjects taking ineffective or partially effective antidepressant therapy will be tapered off their medication. Subjects will be informed about the risks and benefits of discontinuing their established antidepressant medication. If the subject successfully completes the medication taper and continues to meet all study inclusion criteria, a baseline study appointment will be scheduled (Table 2).

Visit 2 – Baseline Visit

At the baseline visit, the study informed consent will be reviewed and signed, and all questions will be answered. A complete psychiatric evaluations and medical history will be obtained, along with a physical examination and laboratory evaluation (including metabolic panel, drug screen and ECG). Any subject with abnormal laboratory results that may constitute a meaningful co-morbid medical illness will be excluded from the trial. Subjects will also have clinical and QOL outcome ratings performed. Subjects will then be randomly assigned to one of the three treatment conditions: *R. rosea* SHR-5 extract 340-1,360 mg daily or sertraline 50-200 mg daily, or placebo.

Visit 3 (Week 2) to Visit 7 (Week 12)

Subjects will return for follow up study visits at weeks 2, 4, 6, 8, and 12. Subjects will be provided with the self-rating instruments designated for that study visit. Subjects will be evaluated by a study clinician to assess the presence and severity of MDD symptoms. The study clinician will also assess the presence and severity of suicidal ideation, and the presence of treatment-emergent AEs (i.e., dates of occurrence, severity, relationship to study drug). A list of concomitant medication will be obtained. A laboratory evaluation (including metabolic panel) will be obtained at Visit 6/WK8 and again at Visit 7/WK12 which is the final visit of the study.

	Visit 1 In Take	Visit 2 Baseline	Visit 3 Wk 2	Visit 4 Wk 4	Visit 5 Wk 6	Visit 6 Wk 8	Visit 7 Wk 12
Consent	X (intake)	X (study)					
Psychiatric & Medical Hx	X						
Physical Exam	X	X (if not yet done)					
Laboratory (incl thyroid)	X					X	X
ECG	X	X (if not yet done)					X
Urine HCG	X			X			X
SCID	X						
CSHF		X					
HAM-D; CGI, CSSRS; BDI; ISI; BFI		X	X	X	X	X	X
QIDS; PGWB; RUSH		X					X
ETI; CRBI		X					X
Expectations of SE & TE		X	X				
Adverse Events		X	X	X	X	X	X
Vital Signs; Weight		X	X	X	X	X	X
Dosage Record		X	X	X	X	X	X

Table 2: Schedule of Study Procedures

Primary study endpoints will be change overtime in the mean 17-item HAM-D rating score at endpoint versus baseline. Response will be defined as a ≥ 50% reduction in total HAM-D score at endpoint (versus baseline). Non-response is defined as a < 50% reduction in total HAM-D score at endpoint (versus baseline). Subjects with non-response will be discontinued from the trial and treated as clinically warranted.

Data and Safety Monitoring

General description

This study will be approved by the Institutional Review Board (IRB) at the University of Pennsylvania. All subjects will be fully informed about the study requirements, foreseeable risks, discomforts and adverse events before being consented.

Data and safety monitoring board (DSMB)

In order to assess possible changes in risk/benefit ratio to study subjects and to obtain independent oversight of the study conduct, we will use an external Data and Safety Monitoring Board (DMSB) to oversee the progress of the study. External DSMB study reviews will be conducted at 6-month intervals. The DSMB members will review and monitor the study procedures, study risks, risk/benefit ratio, patient enrollment, number and nature of medication side effects, and any study-related serious AEs (SAEs).

Adverse event monitoring and documentation

The principal investigator and his/her co-investigators will be responsible for monitoring subject safety, onset and resolution of AEs, and medication dispensing and compliance. All SAEs or life-threatening AEs will be promptly reported to the IRB, the DSMB and the FDA.

Data monitoring

A project manager trained in regulatory procedures and experienced in managing clinical and research documentation will be responsible for maintaining the completeness of all source documentation and case report forms (CRF). A study and database manager will verify the accuracy of data recorded on the CRFs in the patient study binder and identify any discrepancies and inconsistencies. Study quality assurance and data checking process will take place in a continuous fashion to maintain the integrity of the data.

Statistical Analysis

Sample size justification

Sample size calculations will be conducted using N query Sample Size software and will be used to obtain estimates of parameters that will be used to justify the sample size requirements for a future, fully powered study. Although the current study will not be specifically powered to detect small, statistically significant differences between treatment conditions, we will be able to identify trends in the data that will assist us in refining or modifying the aims of a future, fully powered study. For the proposed sample size of 48 subjects, (16 per treatment condition), a one-way ANOVA will have 80% power to detect (at the 0.050 level) an average size of 0.46 Standard Deviation (SD) of the primary outcome (17-item HAM-D rating scale) for the differences among the means at the end of the study. This effect size from ANOVA is the standard deviation of the means in the alternative hypothesis. In addition, the detectable between group differences from a two-sample t-test at the 0.05 level is 1 SD for 16 subjects per group. In this preliminary study, we anticipate that we may not observe an average effect size that is larger than (or equal to) 0.46 SD across 3 groups, so that statistical significance will not be achieved. However, we do anticipate that we will at least be able to observe non-significant trends for differences between treatment conditions. The estimated means and standard deviations (SDs) from this project will then be used to power a future, large-scale trial of *R. rosea*, as a follow-up to this pilot study. We also note that should an effect size of 0.46 SD be observed, this would likely represent a clinically meaningful difference in the primary outcome measure.

Statistical procedures

Analyses will be conducted using the latest version of STATA (STATA Corporation, College Station, TX). The primary analyses will be performed on an intent-to-treat basis. Primary analysis will compare change in MDD severity (e.g., HAM-D score) among treatment conditions. Secondary analyses will compare changes in other MDD outcome measures (e.g., CGI/S, CGI/C, BDI), QOL measures (e.g., SCL-90-R; PGWB, DISF), and safety measures (e.g., frequency, severity and durations of AEs, SAEs, study discontinuation) among treatment conditions. The approach for analysis of the primary and secondary outcome measures will be similar. To assess whether treatment groups are similar at baseline, mean outcome measures will be compared at baseline for subjects in the 3 treatment conditions by ANOVA. The primary hypothesis of equality of mean changes in the primary (and secondary) outcome measures across the 3 treatment conditions will be tested using mixed-effects models [35], with post-hoc tests used to identify the groups responsible for any overall significant difference among treatment conditions. For example, if an overall significant difference is found, we would anticipate finding a significant difference between *R. rosea* and placebo, and possibly between sertraline and placebo. The mixed-effects model takes into account within-subject correlations from repeated measurements of HAM-D scores in the same subjects and for missing data points. We will use HAM-D score as the dependent variable and group, visit week, interaction between group and visit week as primary independent variables. Potential covariates include baseline HAM-D score and any variables that demonstrate between-group discrepancy at baseline. The interaction term "Visit week*treatment group" represents the effect of the treatment on change in HAM-D scores over time.

Similar mixed-effects models will also be used in secondary analysis to compare overall changes in outcome measures among treatment conditions with adjustment for additional covariates. For example, in order to assess the impact of prior MDD treatment on outcome in the present study, subjects will be assessed on the basis of receiving: (i) prior MDD treatment, and (ii) no prior MDD treatment. We will include an indicator term in the models that takes value 1 for patients with a prior treatment and takes value 0 otherwise. Interaction terms will be constructed as the product of this term, the indicator variables for treatment groups and follow-up time. We anticipate that patients with no prior therapy will have a greater reduction in HAM-D scores [36,37]. If the interaction terms differ significantly from zero, this will indicate that the impact of *R. rosea* therapy depends upon treatment history (e.g., patients without prior MDD treatment may respond more favorably to *R. rosea* therapy).

The comparison between *R. rosea* vs. sertraline will be considered secondary analysis. We will compute Cohen's d as an estimate of effect size. We anticipate that we will not identify significant differences between the two active treatments, rather that our exploratory analyses will suggest that *R. rosea* is not inferior, and is perhaps superior, to sertraline. Our findings will then be further explored in a future larger scale study.

Safety profiles of the treatment conditions will be compared via descriptive analyses and by the Chi-Square test to frequency of AEs among treatment groups.

Discussion

We describe a phase II randomized controlled trial (RCT) to evaluate the short-term safety and efficacy of *R. rosea* for the treatment of mild to moderate MDD.

Although conventional antidepressant therapy has simplified the treatment of MDD, a substantial segment of the world's population remains largely untreated [38]. Despite the widespread use of antidepressant therapy, they have substantial limitations. For example, there is limited clinical data showing that these agents provide consistent benefit (versus placebo) in patients with more mild forms of MDD [39]. Moreover, most RCTs of antidepressant efficacy routinely exclude patients with mild symptoms because of the expectation that conventional antidepressants will provide little advantage over placebo. In addition, treatment-emergent AEs with antidepressants are more likely to occur in less severely ill patients, and often result in treatment noncompliance [40]. Furthermore, conventional antidepressants may suppress, rather than eliminate, MDD symptoms in many patients [41], and there is little evidence to suggest that symptom suppression reduces overall risk of suicide or relapse [42].

Many individuals decline conventional antidepressant therapy for financial, cultural, or personal reasons. As a result, many individuals seek alternative remedies for relief of their symptoms. Because depressive symptoms are among the most common reasons for consumers choosing alternative therapy [43], the identification of effective botanicals for MDD is of public health relevance. This is particularly important among the uninsured individuals, certain ethnic and immigrant populations, and for people who decline conventional AD therapy because of its association with mental weakness and social stigma [44-46].

Although a number of botanicals and dietary supplements have been proposed as antidepressants [47-51], there has been a relative paucity of RCTs in MDD. As a result, it is important to rigorously test promising botanical agents for MDD – especially if the botanical has a favorable tolerability profile (versus conventional antidepressants), is potentially effective across a range of illness severity, and is cost effective and simple to use in a non-medical setting.

In summary, the goal of this study is to expand our knowledge of the treatment of MDD by examining: (i) the efficacy of *R. rosea* extract (versus sertraline or placebo) as a CAM treatment for MDD; (ii) the maximum tolerable dose of *R. rosea* extract (versus sertraline) for MDD; and (iii) the safety and efficacy of *R. rosea* extract (versus placebo) over a 12-week period. The protocol can serve as a template for future RCTs to investigate the preliminary effect and safety of natural products for mental health conditions.

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Author Contributions

All authors participated in study design, writing, and final approval of the final manuscript.

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Conflicts of Interests

All the authors had no conflict of interest to declare.

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