A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy of Eleutherococcus Senticosus for Anti-inflammation and Improvement of Erythropoietin Hyporesponsiveness in Subjects Under Renal Dialysis

Study Objectives

The purpose of this study was to investigate the efficacy of the oral Eleutherococcus Senticosus extract on anti-inflammation and improvement of erythropoietin hyporesponsiveness in renal dialysis patients. Inflammation indicators, anemia indicators, and health indicators will be evaluated and compared between the experimental and placebo groups. Safety data and adverse events will also be assessed and compared between the two groups.

Study Design

This is a randomized, double-blind, placebo-controlled, parallel comparison trial to evaluate the efficacy and safety of Eleutherococcus Senticosus taken orally by patients under regular dialysis. Eligible subjects with written consent were randomized into one of the two groups: A. Acanthopanax senticosus (30mg/vial); B. Placebo. After 2-4 weeks of run-in period, the study subjects were asked to take the investigational products orally for 90 days in order to evaluate the effects of oral Eleutherococcus Senticosus liquid on the markers of inflammation, anemia, and safety, and to compare the efficacy between oral Acanthopanax senticosus and placebo groups.

Group	Condition	Sample size
A	*Acanthopanax senticosus* (30mg/vial)	10
B	Placebo	10

Inclusion Criteria

1. Under regular dialysis for at least 3 months
2. Hemoglobin (Hb) <11 g/L after regular Erythropoietin (EPO) treatment
3. Subjects with written informed consent form

Exclusion Criteria

1. Use of steroid or high dose of antiplatelet drug (e.g. Aspirin >300mg) within one month
2. Had surgery, myocardial infarction, or tumor within 12 weeks
3. Currently use of antibiotic treatment for acute infection
4. Pregnant women
5. Reticulocyte>40 x 10^9
6. Anemia (ferritin <100ng/mL and Transferrin Saturation (TSAT) <20%)
7. Urea reduction ratio <65% or single pool Kt/V < 1.0 (hemodialysis patients) or total weekly Kt/V<1.7 (peritoneal dialysis patients)
8. Sudden change of eating habit within one month
9. Expected life less than six months or with unstable medical conditions
10. Known history of allergic reaction to the investigational products
11. With acute diseases and judged by the investigator to be ineligible to participate
12. Received melatonin, androgen therapy or blood transfusion within two months
13. Received any trial medications within 30 days

When the subject withdraws from the study for any reason, the researcher should try his best to understand the reason why any subject withdraws, and the relevant information should be recorded in the case report, and the researcher still needs to encourage all the subjects to complete the last visit. All assessments help to understand or identify measures to avoid untoward effects and to seek appropriate solutions to any difficulties.

Investigational Product

Acanthopanax senticosus (30mg/vial) and Fructus Ziziphi Jujube concentrated juice15ml/vial used in this study were manufactured and provided by Direct Biotechnology Corp. Using Fructus Ziziphi Jujube concentrated juice15ml/vial as placebo is to make it the same flavor as the experimental group. The investigational product has been tested by SGS for nutritional composition analysis, which confirms that this product has very low potassium and phosphorus content, which is

extremely safe for patients with dialysis.

Suggesting use:

One bottle daily, can be taken before and after meals. Take a small bite in the mouth for a while before swallowing. Do not drink water for 20 minutes after consumption to achieve the fastest absorption. Patients with hyperacidity and gastroesophageal reflux are recommended to take it after meals.

Available size: 15ml x 10 bottles

Outcome measures

Laboratory tests including indicators of inflammation, anemia, nutritional status, health status and safety, as well as blood pressure, heartbeat, weight will be tested during the screening period (before consumption) and three months after consumption. The subject's subjective self-assessment questionnaire for the investigational products was completed at each visit after the initiation of consumption. The subjects will also be required to inform the researcher of any adverse events at any time during the study and accept the necessary treatment to ensure the subject safety.

Primary Outcomes

(1) Total used amount of Erythropoietin (EPO)

(2) Inflammation indicators: C reactive protein (CRP), Tumor necrosis factors (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1)

(3) Anemia indicators: hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, reticulocyte count

Secondary Outcomes

(4) Nutritional status: albumin, prealbumin, ferritin, Transferrin saturation, TSAT=serum Fe/TIBC, Total Iron Binding Capacity (TIBC)

(5) Health status: body mass index (BMI), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), fasting glucose, vital signs

Safety evaluations

(6) GOP, GPT, creatinine, blood K, blood P, intact parathyroid hormone (iPTH)

Vital signs and body weight

Blood pressure and heart beats will be measured twice after at least 5 minutes rest at every visit with 5 minutes interval, and the average values will be recorded. Body weight and height will also be assessed at each visit.

Subject's subjective self-assessment questionnaire

The subjective assessment of the test subject was evaluated with a self-administered questionnaire:

1. As of now, test products are positive for your condition? □Yes □No
   List the positive effects of test products on your body? _____
2. As of now, test products for adverse effects on your body? □Yes □No
   List the adverse effects of test products on your body? _____

Study flow chart

Renal dialysis is a regular process. Patients will return to the hospital regularly for dialysis. In addition to the necessary medical treatment, each time they return to the clinic, they will be issued with the needed amount of the investigational products before the next visit, and the empty bottles and records will be collected. Other important follow-up time points are as follows:

Visit	1	2	3	4
Week	-2~-4	0	4	13
Day	-14~-30	0	30±3	90±3
Informed Consent	X			
Medical History	X			
Eligibility	X	X		
All evaluated indicators/Lab tests	X			X
Blood pressure, height and weight	X	X	X	X
Dispense Study Product		X	X	X
Accountability			X	X

Concomitant medication	X	X	X	X
Patient Questionnaire / Adverse Event			X	X

Note:

1. If Hb is still lower than 8g / L after receiving conventional erythropoietin treatment and test products, blood transfusion treatment should be given
2. The clinical care aims to maintain the subject's hemoglobin at 11-12 g / L
3. Dates and doses of subjects receiving blood transfusions or iron during the trial must be recorded.

Statistical Analysis

Means and standard deviation are presented for continuous data, while frequency and percentage are used for categorical variables. All laboratory and vital evaluations were then compared between the two groups using the Mann-Whitney U test. Fisher's exact test was performed for comparison of categorical variables. The Wilcoxon signed-rank test was performed to compare the values at baseline and 3 months after the initiation of product administration to each group. Statistical analyses were conducted by the study statistician with SPSS Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered to be statistically significant.