
Clinical Trial Effects of *Apocynum venetum* Leaf Extract on Depression and Anxiety {Hamilton Depression Rating Scale}

Summary

A double-blinded, randomized parallel group pilot study was conducted showing the effects of *Apocynum venetum* Leaf Extract on symptoms of depression in individuals with mild depression. The study began in August 2005 and ended in May 2006. Once the last subject was recruited, final results were compiled. This trial revealed that *Apocynum venetum* Leaf Extract may be considered a beneficial alternative for those who experience mild depression and suffer from anxiety.

Study Participants and Protocol

In order to be included as a participant in the trial, several criteria had to be met. Both men and women, between the ages of 18-65 years, were eligible. At the initial screening visit, a signed consent form was obtained. Mild depression was determined through the use of the Hamilton Depression Rating Scale (HAM-D) — a multiple choice questionnaire that rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety, and weight loss. Originally developed in 1960, it is one of the most widely used and respected clinical scales for rating the severity of depression in medical research. Those who fulfilled the inclusion criteria for mild to moderate depression (a total score in the range of 14-20 on the HAM-D 17-item version), but with a maximum score of 1 on HAM-D Question 3 (regarding suicidality) were asked to undergo a physical examination by the study physician.

Potential subjects were required to be deemed healthy, which was determined by a physical examination and blood chemistry panels. The physical examination included blood pressure and anthropometric measurements as well as health

tests {glucose, urea, creatinine, sodium, potassium, chloride, TSH, bilirubin, Alk Phos, AST, SGOT, SGPT, total protein, CBC, hemoglobin, RBC, WBC, and platelets}. Body Mass Index (BMI) — a measure of body fat based on height and weight — had to be in the range of 18-35 kg/m² to be considered. Upon confirmation that the individual was mildly depressed, but healthy, and eligible according to blood tests, an appointment was arranged for the study to commence.

The exclusion criteria included:

- Non-compliance
- Anticipated problems with product consumption
- Moderately severe co-morbid disease (including cardiac, pulmonary, renal, hepatic, active cancer, diabetes, hypertension, immunological and neurological disease)
- Consumption of nutritional, herbal or prescription product containing St. John's wort, hypericin, hyperforin, hyperoside or isoquercitrin within the past 30 days
- High alcohol intake {more than two drinks per day}
- Pregnant or breastfeeding
- Use of antidepressant prescription medication
- Use of herbal products within one week before the study

Sixty-six subjects were assessed for eligibility; 47 were enrolled in the study. At baseline (Day 0), eligible subjects were randomly divided, using randomization tables, into two groups — the *Apocynum venetum* Leaf Extract group was assigned 27 subjects, and 20 were in the placebo group. Subjects were blindly designated to receive an 8-week supply of either *Apocynum venetum* Leaf Extract or placebo. Participants were instructed to take two tablets per day. Subjects were given forms to report weekly

adverse effects, blood pressure was measured, and blood samples were drawn to determine blood neurotransmitters. After 4 weeks had elapsed, HAM-D scores and blood pressure were determined. At the end of the 8-week study period, completed symptom/side effect forms and unused study product were collected. A second blood sample was drawn from study participants for determination of blood neurotransmitters. HAM-D scores and blood pressure were also measured.

Study Results

HAM-D

The primary outcome measured by the trial was the changes in HAM-D score, since it is one of the most commonly used scales for rating depression in medical research. Treatment response is measured by a decreased score on the HAM-D scale. A lower score indicates greater improvement. The overall reduction in HAM-D score was 47.3% in the *Apocynum venetum* Leaf Extract group. The *Apocynum venetum* Leaf Extract group also showed a significant difference in HAM-D scores between 4 weeks and 8 weeks of use. Improvements were noted in the *Apocynum venetum* Leaf Extract group in certain individual questions; the most notable being an improvement in the rating for Question 1 (depressed mood).

After 8 weeks of treatment, 40% of the subjects in the *Apocynum venetum* Leaf Extract group showed greater than a 10-point decrease in HAM-D scores. It should also be noted that 50% of the *Apocynum venetum* Leaf Extract group showed a decrease in HAM-D score of 50% or greater. Also, 60% of the *Apocynum venetum* Leaf Extract group had a HAM-D score of 8 or less by week 8. This analysis demonstrates overall improvement from baseline.

Insomnia

Other individual questions which resulted in significant improvements within the *Apocynum venetum* Leaf Extract group included insomnia middle, insomnia late, work and activities, anxiety (somatic) between baseline and Week 8. There was a trend toward a decrease in insomnia in the *Apocynum venetum* Leaf Extract group. The average mean insomnia score was reduced by 60% in the *Apocynum venetum* Leaf Extract group. This suggests that *Apocynum venetum* Leaf Extract may offer a benefit to certain individuals.

Hamilton Depression Rating Scale	Treatment (n=20) <i>Apocynum venetum</i> Leaf Extract
Baseline Score, Mean (SD)	16.4 (1.9)
Week 4 Score, Mean (SD)	11.7 (4.2)
Week 8 Score, Mean (SD)	8.7 (4.4)
Change From Baseline Score, Mean (SD)	7.75 (4.96)
% Reduction	47.3%

Change in Score on Hamilton Depression Rating Scale	Treatment (n=20) <i>Apocynum venetum</i> Leaf Extract	
	0 - 4 Weeks	4 - 8 Weeks
≥ 50% Decrease	5 (25.0%)	4 (20%)
≥ 20% Decrease	13 (65.0%)	13 (65%)
≥ 10% Decrease	3 (15.0%)	2 (10%)

	Treatment (n=20) <i>Apocynum venetum</i> Leaf Extract
HAM-D Responders at Week 8 (≥ 50% Decrease)	10 (50%)
Change in HAM-D at Week 8 Score (≥ 20% Decrease)	16 (80.0)
Change in HAM-D at Week 8 Score (≥ 10% Decrease)	8 (40%)
HAM-D Score of 8 or Less at Week 8 Score	12 (60%)
HAM-D Score of 6 or Less at Week 8 Score	7 (35%)

Hamilton Depression Rating Scale	Treatment (n=20) <i>Apocynum venetum</i> Leaf Extract
Baseline Score on Insomnia, Mean (SD)	3.60 (1.50)
Change From Baseline Score, Mean (SD)	2.15 (1.50)
% Reduction	60%

Blood Neurotransmitters

This study measured blood neurotransmitters as a secondary outcome. Blood neurotransmitters, such as platelet serotonin and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), may be markers associated with depression. Although increased platelet serotonin has been suggested to be indicative of increased neuronal serotonin, and medical treatment may positively affect these levels, it is not clear whether MHPG concentrations are modified by all conventional medical treatments.

Serotonin

Further analysis revealed that 50% of subjects in the *Apocynum venetum* Leaf Extract group responded to *Apocynum venetum* Leaf Extract in terms of increased serotonin levels (increase of 67%; 10.6 ± 6.3 ng/ml to 17.7 ± 7.2 ng/ml). Of the 20 subjects in the *Apocynum venetum* Leaf Extract group, 35% showed an increase of at least 20%.

MHPG

A decrease of MHPG levels in 65% of subjects in the *Apocynum venetum* Leaf Extract group (decrease of 41%; 3.3 ± 2.9 ng/ml to 1.9 ± 1.8 ng/ml). These changes were significant ($p < 0.05$) within the responders of the *Apocynum venetum* Leaf Extract group.

Safety

Apocynum venetum, the leaves from which *Apocynum venetum* Leaf Extract are made, has a long history of safety. *Apocynum venetum* was used as a tea for hundreds of years in traditional Chinese medicine. The leaves have also been demonstrated to be nontoxic in an acute toxicity study on mice. Six case reports showing that subjects with depression who took 50 mg. of *Apocynum venetum* Leaf Extract per day for periods ranging from 2 weeks to 3.5 years did not experience any adverse reactions.

Adverse Effects

Safety was one of the objectives of this study after taking *Apocynum venetum* Leaf Extract for 8 weeks. The results of this study suggest that the use of *Apocynum venetum* Leaf Extract by individuals with mild depression is safe, since no severe adverse effects were reported. No subject dropped out of the study due to side effects.

Blood Pressure

Analysis of blood pressure at baseline, 4 weeks and at the end of the study showed no significant changes. However, these results demonstrate the lack of effect of *Apocynum venetum* Leaf Extract on blood pressure, and support its safe use.

Summary

The significant improvement within the *Apocynum venetum* Leaf Extract group for Question 1 (depressed mood) on the HAM-D questionnaire suggests a potential benefit of *Apocynum venetum* Leaf Extract in a population of individuals with mild depression. As indicated above, more subjects in the *Apocynum venetum* Leaf Extract group showed a decrease in the HAM-D score of at least 50%, as well as a final score of less than 8. These analyses demonstrate overall improvement from baseline in the *Apocynum venetum* Leaf Extract group.

Additionally, 50% of subjects in the *Apocynum venetum* Leaf Extract group responded to *Apocynum venetum* Leaf Extract in terms of increased platelet serotonin, 35% of which showed an increase of at least 20%; and MHPG decreased in 65% of subjects in the *Apocynum venetum* Leaf Extract group. As discussed above, changes in platelet serotonin may indicate neuronal changes. Thus, an increase in serotonin of 67% suggests a possibility of increased neuronal serotonin and thus the potential to offer clinical benefits. It is unclear, what effect if any, a decrease in plasma MHPG has on clinical benefits.

It has been reported in the scientific literature that treating patients with mild or moderate depression is difficult. These patients may not be suitable candidates for medications such as SSRIs and tricyclic antidepressants, partially due to the side effects associated with them. A product which has antidepressant effects, with a lower risk of serious side effects, would be preferable to most individuals.

This was a small pilot trial and may not have been adequately powered to detect significant changes. The fact that the *Apocynum venetum* Leaf Extract group showed positive trends given the small sample size is indicative of the potential benefits for mild depression. Given the promising effects in some of the study participants, *Apocynum venetum* Leaf Extract may be considered as an alternative for patients with mild depression.