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File: ■ Rhodiola (*Rhodiola rosea*, Crassulaceae)
■ Sertraline
■ Major Depressive Disorder

HC 062052-659

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RE: Co-administration of Rhodiola with Sertraline Produced a Significant Antidepressant Effect in Patients with Mild-to-moderate Depression

Gao L, Wu C, Liao Y, Wang J. Antidepressants effects of Rhodiola capsule combined with sertraline for major depressive disorder: A randomized double-blind placebo-controlled clinical trial. *J Affect Disord*. March 15, 2020;265:99–103. doi: 10.1016/j.jad.2020.01.065.

Rhodiola (*Rhodiola rosea*, Crassulaceae) root is an adaptogen—increases the body's ability to adapt to stress— and has been reported to have antidepressant and anxiolytic activity. It is used in traditional medicine as a health-enhancing supplement. The major active constituents are thought to be salidroside (rhodioloside) and rosavin. The purpose of this randomized, placebo-controlled, study was to evaluate the feasibility of an efficacy and safety study of just the Rhodiola Capsule (a proprietary Chinese medicine by Tibet GaoYuanan Biotechnology Co, Ltd; Tibet, China) as an antidepressant.

Patients (n = 100, aged 18-50 years) diagnosed with mild-to-moderate major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV Axis I) were recruited from the Department of Neurology and Psychiatry at the second Affiliated Hospital of Fujian Traditional Chinese Medical University; Fujian, China, and via advertisements in WeChat and newspapers. Included were patients that met the following criteria: healthy according to medical history, vital signs, and results of routine laboratory tests; scored > 12 on the Hamilton Depression Rating (HAM-D; version not specified); scored 3 (mild) or 4 (moderate) on the Clinical Global Impression Change (CGI/C); agreed to use suitable methods of contraception during the study and for three months afterwards; were non-smokers; and signed informed consent. Excluded patients had a current diagnosis of severe MDD; were pregnant or breast feeding; had bipolar disorder; were blind; had psychosis; had substance abuse or dependence disorder within the preceding three months; used antidepressant, mood stabilizer, or antipsychotic drugs within five elimination half-lives of starting study drug; had a positive alcohol breath test at any visit; had primary anxiety disorder; were currently participating in another clinical trial, or participated in another clinical trial within the previous three months; women of child-bearing potential not using a medically acceptable form of contraception; were using concurrent herbs, remedies, or mineral supplements (except

mineral supplements prescribed for medical purposes); used chemotherapy or other medication known to produce mood changes; had sensitivity to rhodiola or sertraline; history of nonresponse to sertraline or rhodiola; or used monoamine oxide (MAO) inhibitor within 14 days of starting study drug.

Patients were randomized to one of the three following groups for the 12-week treatment: (1) sertraline (Pfizer Pharmaceuticals Limited) plus two placebo capsules (lactose monohydrate), (2) sertraline plus two Rhodiola Capsules (0.6 mg/day, high dose), or (3) sertraline plus one placebo capsule and one Rhodiola Capsule (0.3 mg/day, low dose). The dose of sertraline was not specified. Rhodiola Capsule is a standardized root extract, containing salidroside, microcrystalline cellulose, silicon dioxide, and magnesium stearate. The primary outcome measure was the change in HAM-D score compared to baseline. The secondary outcome measures were the change in CGI/C score and Beck Depression Inventory (BDI) score compared to baseline. Blood pressure, pulse, and weight were obtained at each study visit.

There were no significant differences in demographics, mean HAM-D score, and mean BDI score between groups at baseline (baseline differences for CGI/C were not reported). Both Rhodiola Capsule groups had a significant improvement in HAM-D, BDI, and CGI/C compared with the sertraline only group at six weeks ($P < 0.05$, $P < 0.05$, and $P < 0.01$; respectively) and 12 weeks ($P < 0.01$ for all). The improvement with the high dose group was significantly greater than the low dose group ($P < 0.05$) on HAM-D, BDI, and CGI/C. Patients taking rhodiola with sertraline had a lower rate of adverse events (AEs) compared with those taking sertraline with placebo. No serious adverse events were reported. There were no clinically meaningful changes in systolic and diastolic blood pressure, pulse rate, weight, or laboratory parameter in any group.

The Rhodiola Capsule (0.3 and 0.6 g/day) produced a significant antidepressant effect in patients with mild-to-moderate depression when administered with sertraline for 12 weeks. In particular, there were improvements in insomnia, emotional instability, and somatization (= physical complaints). There were no AEs attributed to rhodiola. The mechanism of action is unknown. The feasibility of doing a study in depression using Rhodiola alone is suggested by these data. A limitation is that the authors did not report the dose of sertraline used, so the study cannot be replicated. The authors report no conflicts of interest.

—Heather S. Oliff, PhD