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File: ■ Ashwagandha (*Withania somnifera*, Solanaceae) Root
■ Anxiety
■ Systematic Review

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RE: Systematic Review of Ashwagandha for the Treatment of Anxiety

Pratte MA, Nanavati KB, Young V, Morley CP. An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (*Withania somnifera*). *J Altern Complement Med*. 2014;20(12):901-908.

Ashwagandha (*Withania somnifera*, Solanaceae; WS) root is used in Ayurvedic medicine as a broad-spectrum remedy or tonic, and has been shown to have anti-inflammatory, antioxidant, and anxiolytic properties. The purpose of this systematic review was to evaluate human studies of WS as a treatment for anxiety.

The PubMed, SCOPUS, CINAHL, Google Scholar, Google, and AYUSH Research Portal databases were searched using the key words ashwagandha or withania in combination with mental health terms such as anxiety, behavior, mood, and stress. The searches were limited to English language reports of randomized, controlled clinical trials evaluating WS as a treatment for anxiety. Studies investigating formulas containing WS, review articles, and duplicate publications were excluded.

Five studies met the inclusion/exclusion criteria. Validity and risk of bias for each study was evaluated using the Cochrane Collaboration risk-of-bias tool. A meta-analysis could not be conducted because the trials had different primary outcome measures and durations (six to 12 weeks), and evaluated different doses (12,000 mg/day raw herb, 125-2,500 mg/day extract), dosage schedules (one to three times daily), and formulations (raw root, ethanol extracts, or water extracts containing 1.5%, 5%, or 12% withanolides).

One study evaluated 39 patients who were treated with 500 mg twice daily (1000 mg/day) of placebo or WS root ethanol extract (manufacturer and composition not reported) for six weeks. The dose was increased every two weeks as necessary, up to a maximum of 2,500 mg/day. There was a significant improvement on the Hamilton Anxiety Scale (HAM-A) in the WS group compared with the placebo group ($P = 0.026$). The risk of bias was rated as high. Limitations of the study were the relatively small sample size and short study duration, inconsistent dosing (500-2,500 mg/day), and 48.7% drop-out rate.

The second study included 130 patients who were treated with 125 mg/day or 250 mg/day Sensoril® (Natreon Inc; New Brunswick, New Jersey); 500 mg/day Essentra® (NutraGenesis LLC; Brattleboro, Vermont); or placebo for 60 days. The Sensoril and Essentra products contained root and leaf material derived from a withaferin A and withanolide glycoside-predominant genetically uniform WS chemotype and extracted using a water-based protocol. The product composition cited in the review (minimum of 8% withanolide glycosides and 32% oligosaccharides) is not consistent with the data reported in the original article (11.90% withanolide glycosides, 1.05% withaferin A, and 40.25% oligosaccharides). There was a significant WS dose-dependent increase on the modified HAM-A ($P < 0.001$) compared to placebo. The risk of bias was rated as unclear. Limitations of the study were the 24.6% drop-out rate and potential reporting bias (two authors were employed by the company funding the trial).

The third study included 81 patients who were treated with naturopathic counseling plus 300 mg twice daily (600 mg/day) WS root extract standardized to 1.5% withanolides (manufacturer not reported) or psychotherapy plus placebo for 12 weeks. Beck Anxiety Inventory scores significantly improved in the WS group compared with the placebo group ($P < 0.0001$). The risk of bias was rated as high. Limitations of the study were the 21% drop-out rate, the lack of a true control group, and potential performance bias because the therapists could not be blinded.

The fourth study included 64 patients who were treated with 300 mg twice daily (600 mg/day) WS root extract containing at least 5% withanolides (KSM-66®; Ixoreal Biomed; Hyderabad, Telangana, India) or placebo for 60 days. KSM-66 is produced using an alcohol-free and synthetic solvent-free "green chemistry" extraction process. There was significant improvement on the Perceived Stress Scale and in cortisol levels in the WS group compared with the placebo group ($P < 0.0001$ and $P = 0.0006$, respectively). The risk of bias was rated as unclear. A limitation of the study was the relatively small sample size.

The fifth study included 86 patients who were treated with anupana (milk) plus 4 g raw WS root (source not provided) or placebo three times daily (12,000 mg/day) for 60 days. To prepare the WS treatment, dried root was pulverized, combined with equal quantities of sugar syrup, sieved (40#), and dried to create granules (chemical composition/standardization was not reported). Changes in HAM-A scores were not significant compared with placebo, except for the anxious mood domain ($P < 0.001$). The risk of bias was rated as unclear.

All five studies concluded that WS was safe. Adverse events in the WS groups were mild and did not differ in frequency or duration compared with the control groups.

In summary, WS significantly improved measures of anxiety compared to the control in most trials. However, most of the studies were methodologically flawed and underpowered, and none attained a low risk-of-bias rating. In addition, the primary outcomes for all of these studies were patient-reported measures. The authors suggest that the addition of objective data obtained from blinded diagnostic interviews and the assessment of biomarkers would strengthen future studies. They also point out several limitations of this review, including the exclusion of studies published in other languages and trials evaluating the traditional use of WS (Ayurvedic formulas containing WS).

The authors conclude that while these "somewhat promising but early, and possibly biased, results" suggest that WS may significantly improve symptoms of stress, "additional research in larger samples and in more clinical contexts is essential to validate its therapeutic capabilities for widespread use." In addition, the optimal WS preparation form, chemical composition, dose, and dosage schedule for the treatment of anxiety remains to be determined.

—Heather S. Oliff, PhD

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