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File: ■ Kava (*Piper methysticum*)
■ Anxiety
■ Depression

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RE: Aqueous Extract of Kava Found Anxiolytic Even in Depressed Subjects

Sarris J, Kavanagh DJ, Byrne G, Bone KM, Adams J, Deed G. The kava anxiety depression spectrum study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*. *Psychopharm*. May 9, 2009: [epub ahead of print] DOI: 10.1007/s00213-009-1549-9.

It has been demonstrated that kava (*Piper methysticum*) extracts are effective anxiolytic agents. However, concerns over hepatotoxicity have led to removal or restriction of use of kava preparations in many countries, reducing the few effective options for treating anxiety. The World Health Organization (WHO) recommended that kava products from traditional water-based suspensions should be developed and tested. WHO hypothesizes that aqueous extracts may be effective for mood disorders and have less safety issues. Thus, the purpose of this study was to determine the efficacy and safety of an aqueous extract of kava in treating anxiety and depression. This study, called the Kava Anxiety Depression Spectrum Study (KADSS), is the first published clinical trial testing effects of an aqueous extract of kava on anxiety and/or depression and the first to test whether levels of depressive symptoms affect its anxiolytic effect.

Sixty patients with anxiety (>10 on the Beck Anxiety Inventory) participated for at least 1 month in this randomized, double-blind, placebo-controlled crossover study conducted at the University of Queensland, Australia. Patients were not required to have a diagnosis of generalized anxiety disorder, though 66% did share this diagnosis. Patients with a history of psychosis, bipolar disorder, or suicidal ideation in the previous 6 months were excluded. Participants were first given liver function tests and placebo for a 1-week run-in phase. Those who had evidence of liver dysfunction (n=3) or a ≥ 50% reduction in anxiety during this phase (n=14) were eliminated from the study; 2 others withdrew. Remaining participants received either kava or identical placebo tablets for 1 week, and then they were crossed-over to the opposite treatment. Patients consumed 5 kava aqueous extract tablets (MediHerb; Warwick, Australia) each day in divided doses, containing a total of 250 mg of kavalactones each day. This dose was the maximum dose approved in Australia. Patients were assessed with the Hamilton Anxiety Scale (HAMA, primary outcome measure), the Montgomery-Åsberg Depression Rating Scale (MADRS), Beck Anxiety Inventory (BAI), and Beck Depression Inventory-II (BDI-II).

Nineteen patients were excluded from the study following the run-in phase, so a total of 41 patients participated in the crossover phase. During the first controlled phase, for the primary outcome measure, the aqueous extract of kava reduced HAMA 9.9 points below baseline compared with 0.8 points for placebo. During the second controlled phase, the group that received kava had a reduction of 10.3 points compared with an increase of 3.3 points for the group that received placebo. The weighted mean was a reduction of 11.4 points during kava treatment. A pooled analysis (using differences from pretreatment scores) showed that kava very significantly improved anxiety ($P < 0.0001$). The clinical response rate ($\geq$ 50% reduction on HAMA below baseline) was 62% (23/37), while the remission rate ($\leq$ 7 on HAMA) was 35% (13/37) for kava. The pooled analysis for BAI also demonstrated that kava was significantly more effective then placebo ($P = 0.001$). Likewise, kava produced a significant improvement in depression levels compared with placebo as measured by the MADRS ($P = 0.003$).

There were no serious adverse effects from kava. There was 1 mild case of nausea that began with kava treatment and ended 1 day after it was stopped and resulted in the patient discontinuing the study. Another patient also had mild infrequent nausea during the kava phase. The authors believe that the nausea was attributed to the amount of dihydromethysticin in the extract. They hypothesize that a cultivar with a lower amount of dihydromethysticin would reduce the risk of nausea. There were no clinical signs of hepatotoxicity during the study.

The authors state that the outcome on the HAMA is comparable to that of benzodiazepines with fewer dropouts than in studies with benzodiazepines. Also, as opposed to benzodiazepines that cause insomnia, agitation, etc. when discontinued, kava cessation did not produce rebound symptoms.

A novel component of this study was the evaluation of the effect of kava on depression. The German Commission E advises against prescribing kava for depression; however, there have been no previous studies evaluating kava for depression that utilize depression outcome scales. The results of this study showed: (1) kava did not induce depression, (2) the baseline depression level was not predictive of response on HAMA, and (3) kava had an acute antidepressant effect according to the MADRS.

An acknowledged limitation of the study is that the treatment duration was too short to make definitive conclusions about efficacy or safety. For this reason, the authors state aqueous extracts of kava should be used short-term or with intermittent use. An empirical limitation is the mixed sample population (different anxiety disorders, different levels of anxiety, etc.). Nonetheless, the study supports the efficacy of aqueous extracts of kava in a real-world setting (i.e., mixed population) even though the data cannot speak to a specific patient population. These provocative findings should be viewed as preliminary until larger and longer studies involving periodic clinical examinations and liver function tests are conducted to support this efficacy and safety data.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.