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**File: ■ Kava (*Piper methysticum*)**
**■ Generalized Anxiety Disorder**
**■ Hepatotoxicity**

**HC 031351-470**

**Date: April 15, 2013**

**RE: Kava for the Treatment of Generalized Anxiety Disorder Shows Efficacy and No Adverse Effects in Liver Function**

Sarris J, Stough C, Teschke R, et al. Kava for the treatment of generalized anxiety disorder RCT: Analysis of adverse reactions, liver function, addiction, and sexual effects. *Phytother Res*. January 24, 2013; [epub ahead of print]. doi: 10.1002/ptr.4916.

Evidence suggests that kava (*Piper methysticum*) is efficacious; however, cases of hepatotoxicity have led to its withdrawal or restricted use in many Western countries. Considering that kava has benzodiazepine-like effects, questions arise as to whether kava is addictive, has adverse sexual side effects, or has withdrawal effects. Hence, the purpose of this randomized, double-blind, placebo-controlled study was to evaluate adverse events (AEs), withdrawal/addiction effects, and liver function effects associated with kava use in patients with generalized anxiety disorder (GAD). Also, genetic polymorphism of the liver enzyme cytochrome P450 2D6 (CYP2D6), which metabolizes kava, was evaluated to determine whether subjects who were poor or extensive metabolizers have different AEs.

Patients (n = 58; aged 18-65 years) with *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) diagnosed GAD were recruited from the Greater Melbourne area in Victoria, Australia via mass media. Excluded patients had major depressive disorder or elevated depressive symptomatology (> 17 on the Montgomery-Asberg Depression Rating Scale); a *DSM-IV* diagnosis of a psychotic or bipolar disorder illness; significant suicidal ideation in the previous 6 months; current use of antidepressants, mood stabilizers, antipsychotics, opioid analgesics, or St. John's wort (*Hypericum perforatum*); diagnosed hepatobiliary disease/inflammation; substance abuse or dependency disorder in the previous 6 months; a previous adverse reaction to kava or benzodiazepines; kava or benzodiazepine use in the previous 12 months; or abnormal baseline liver function. The study began with a 1-week placebo run-in phase. Any subject who showed a 50% improvement on the Hamilton Anxiety Scale (HAM-A) score was excluded from the study.

For 6 weeks, patients received placebo or 120 mg of kavalactones/day, which was titrated to 240 mg/day in patients showing no response at 3 weeks. The kava was

formulated from pressed, dried, aqueous peeled rootstock of kava (Integria Healthcare; Eight Mile Plains, Queensland, Australia). At weeks 2 and 7, AEs were assessed via questionnaire, and blood was drawn for liver function tests and to determine polymorphisms.

There were no significant AEs reported. There was 1 case of dermatitis and 1 case of minor stomach upset that were attributed to kava intake. Withdrawal was assessed by treating all patients with placebo for 1 week at study end. There was no significant increase in AEs in either treatment group. Addiction was assessed by evaluating the number of patients who said that they wanted an increase in dose. Both treatment groups had the same number of patients who wanted to increase the dosage. There were no significant differences from baseline in liver function tests, and no patient developed clinical signs of hepatic abnormality. However, gamma-glutamyl transpeptidase (GGT) was elevated in kava-treated patients compared with those who took placebo at week 7 ($P = 0.08$). This finding may be due to an outlier; 1 patient had an isolated increase in GGT. Intermediate or extensive CYP2D6 metabolizer status had no significant impact on the type or frequency of AEs or abnormal liver function tests. Kava did not diminish sexual performance or enjoyment in men and women. However, there was a trend for kava-treated men to have more difficulty reaching orgasm ($P = 0.067$). Kava-treated women had a significant increase in sex drive ($P = 0.04$).

The authors conclude that kava has no deleterious effects on sexual function and pleasure, has no addictive qualities or withdrawal issues, and is safe for patients with GAD when taken for 6 weeks. Patients with GAD would require treatment for longer than 6 weeks, so a longer-term study is needed to confirm the findings. Nonetheless, this study contributes to the growing body of evidence that water-soluble, standardized formulations of kava from noble cultivars are safe. The authors conclude that these data may assist in the reintroduction of kava in restricted markets. This study uses a medicinal dose of kava, and the results cannot be extrapolated to traditional recreational use.

*—Heather S. Oliff, PhD*

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